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A.M.A. JOURNAL OF

# DISEASES OF CHILDREN

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*Richard T. Smith*

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*Ralph W. Massie and Mildred Stahlman*

Infection Following Splenectomy in Infants and Children
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A New Reflex in Young Infants
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Etiologic Factors in Mental Deficiency
*Stanley W. Wright, George Tarjan, Richard W. Lippman, and Thomas L. Perry*

Abstracts from Current Literature

News and Comment

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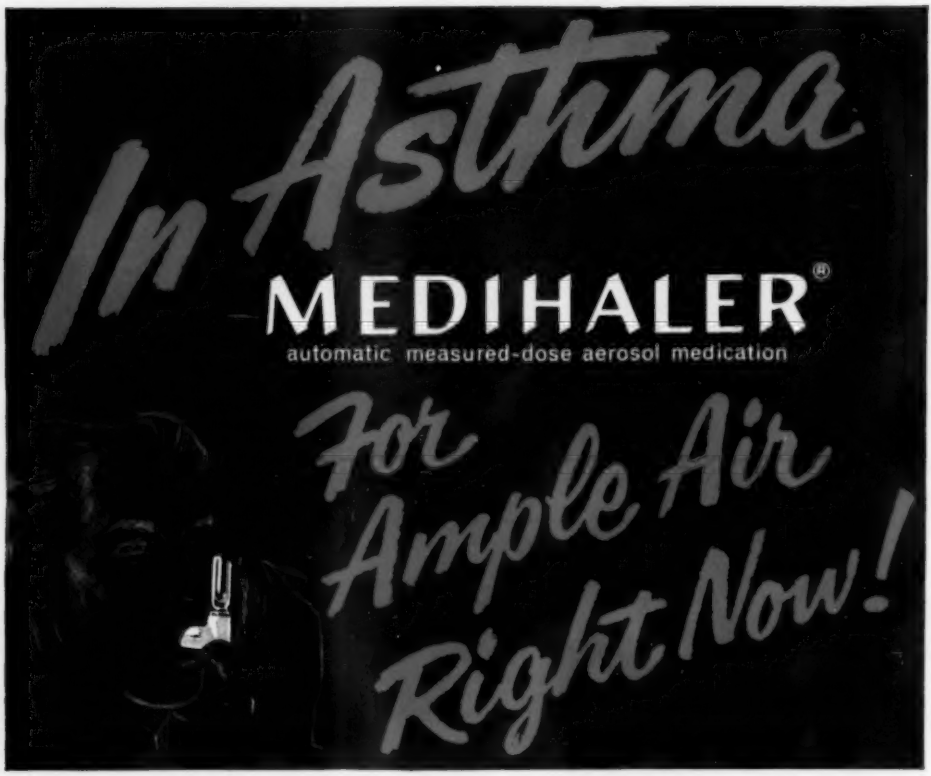


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# Journal of Diseases of Children

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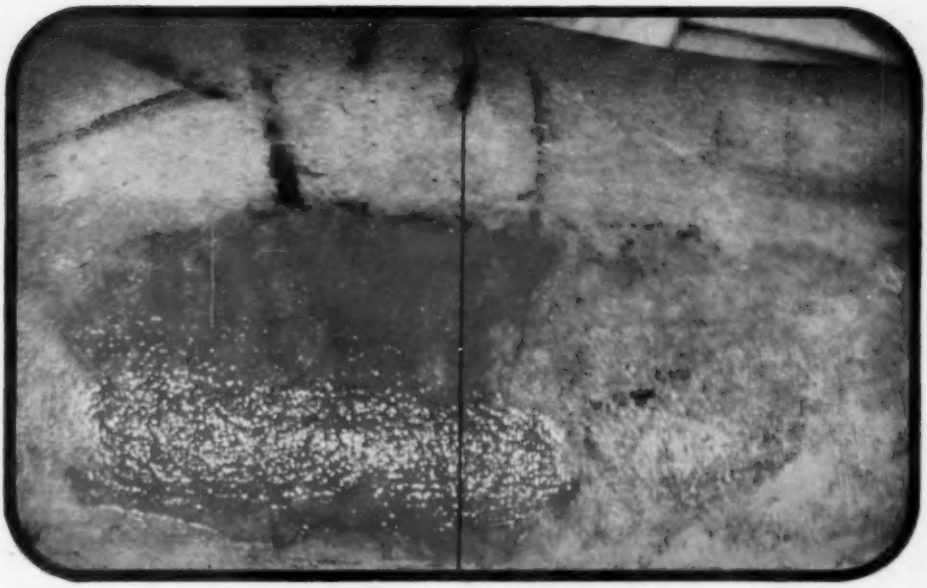

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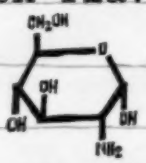


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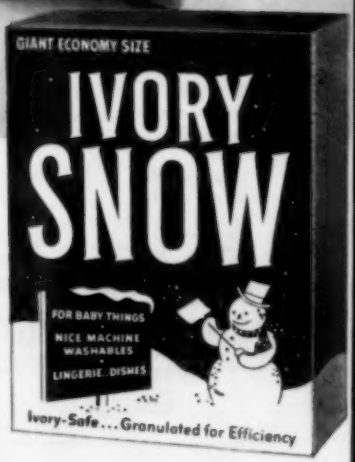


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DISEASES OF CHILDREN

# The Role of a Chronic Carrier in an Epidemic of Staphylococcal Disease in a Newborn Nursery

RICHARD T. SMITH, M.D., Dallas, Texas

Staphylococcal disease is now recognized as a serious and widespread cause of morbidity and mortality in newborn infants and their mothers. The epidemiological studies made possible by bacteriophage typing of this group of micro-organisms have demonstrated that the agent is usually acquired by the infant in the hospital environment, from nursing personnel, from other infants, or possibly from various fomites [1-7] and that the carrier state may persist long after the infant's discharge from the nursery.[8] Virulance as well as ability to produce a nasal carrier state vary greatly with different bacteriophage types of Staphylococcus pyogenes,[9] the most virulant strain reported to date being lysed by phages 42B/47C/44A/52/80/81.[8] Control of epidemics has not been entirely satisfactory; the usual hygienic measures frequently fail to stop the spread of infection,[10] and hexachlorophene bathing or erythromycin treatment [1, 11,12] has been found necessary to arrest certain outbreaks.

This report describes an outbreak of staphylococcal disease which occurred in a newborn nursery and was due to the "epidemic" strain, 42B/47C/44A/52/80/81. This epidemic is noteworthy because identification and elimination of single chronic carrier appeared to result in control of the epidemic; too, no similar single-source outbreak involving the epidemic strain has been documented in the literature. Although many hospital outbreaks are undoubtedly more complex than this one appears, the lessons learned should be of value to others facing similar problems.

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## Material and Methods

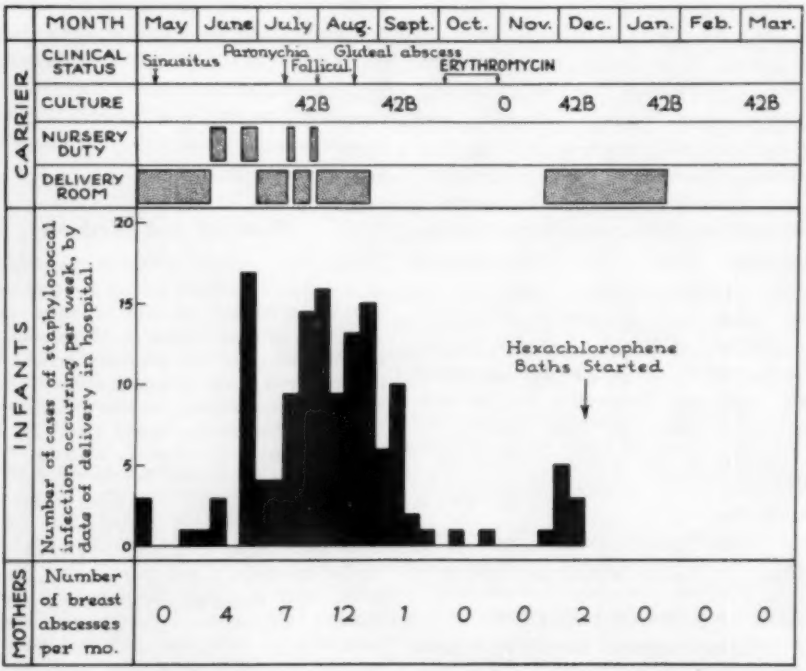
During the summer of 1956 an alarming number of infections in newborn infants and their mothers, both in the hospital and after discharge, occurred at a large general hospital in Minneapolis. Some of these infections were considered serious, but the majority were minor infections with serious potentialities. The hospital records of all newborn infants admitted to the nursery after May 1, 1956, were reviewed to determine the incidence of various infections in the nursery before the start of the epidemiological studies. Physicians on the hospital staff who had delivered infants during the period were contacted to determine the incidence of infection in mothers and their infants up to six weeks after discharge. Some mothers may have changed physicians; therefore additional post-hospitalization infections probably occurred but are not included in these data.

From the beginning of the investigation, all coagulase-positive staphylococci isolated were saved for bacteriophage typing. Since this included strains from lesions occurring up to two months after discharge, the bacteriophage pattern of S. pyogenes presumably acquired earlier in the out-

break could be assessed. Culture of unbroken skin lesions was performed by puncturing the lesions with a 27-gauge hypodermic needle on a tuberculin syringe and aspirating the purulent material after cleaning the area through which the needle passed with hexachlorophene (pHisoHex). The material from the lesions was cultured on rabbit-blood agar plates; Wright- and Gram-stained smears also were examined. A survey of the incidence of staphylococcal colonization of the nasopharynx was conducted on three occasions. A Bradford wire swab was passed into the nasopharynx and allowed to remain approximately 30 seconds; it was then streaked out on a rabbit-blood agar plate. After 24 hours incubation at 37 C the plates were examined, and representative colonies having staphylococcal morphology were picked and tested for clumping in the presence of human plasma. Clumping was assumed to indicate coagulase production. All coagulase-positive staphylococci isolated on the first two surveys were tested with all available bacteriophage types. However, on the final survey, the strains isolated were simply screened for the presence or absence of the lytic pattern of the pathogenic type encountered in the outbreak. The coagulase-positive staphylococci isolated were saved and sent to the Department of Bacteriology, Ohio State University, Columbus, Ohio, where they were typed by methods established in that laboratory.[1,9]

## Description of the Outbreak

The history of this outbreak and its epidemiological features are summarized chronologically in the Figure; each example of clinical staphylococcal disease, whether occurring in the nursery or after discharge, is plotted by date of birth rather than on the date the infection occurred. An increased incidence of pustular or bullous skin lesions in the nursery was first noted in early May, 1956. Prior to that time only sporadic examples of skin lesions had




Chronological presentation of the weekly incidence of clinical staphylococcal infections in infants and the monthly incidence of maternal breast abscesses during an outbreak of staphylococcal disease due to phage Type 42B/47C/44A/52/80/81. Above are presented, for correlation with the events of the epidemic, the data on the chronic carrier, her clinical staphylococcal infections, and whether she was in the delivery room or nursery during the epidemic period. Note that all infections are plotted by the date of delivery of the infant rather than that on which the infection occurred. *42B* indicates isolation of the epidemic strain from the nasopharynx of the carrier.

been recorded. Five infants born during June developed severe pustular pyoderma from which coagulase-positive staphylococci were isolated. During July a rising incidence of lesions occurred, and increasing numbers of breast abscesses were observed in mothers delivered in that month. The peak incidence of skin lesions in infants and breast abscesses in mothers was reached during August. On Sept. 1, 1956, a program of rigid aseptic technique was inaugurated, and an apparently infected nurse was withdrawn from the nursery. Dry-type skin care, which was routinely practiced in this nursery, was continued, however, and no prophylactic antibiotics were administered to the infants in the nursery. With these measures alone the incidence of disease in the nursery dropped abruptly, the incidence of breast abscesses fell to zero, and no more late infections were known to occur in infants after discharge from the hospital.

After two months of relative freedom from disease staphylococcal skin infection was observed in an additional group of five infants and two mothers developed breast abscesses. The temporal relation of this second group of cases to the reintroduction of the infected carrier is seen in the Figure and is discussed in more detail below. After this secondary peak, dry care was abandoned and washing with hexachlorophene every other day was adopted, as has been urged by several groups of investigators.[1,9,11,13] With this measure, no further cases of staphylococcal disease due to the epidemic strain occurred.

### Clinical Features of the Infections

Most infections which developed in the newborn nursery consisted of 1 to 10 pus-filled bullae on the skin, located usually in the axillary, inguinal, or neck skin folds. Microscopic examination of the exudate from these lesions revealed polymorphonuclear neutrophils and contained many Gram-positive cocci, which on culture proved to be S. pyogenes var. aureus.

TABLE 1.—*Summary of Clinical Features of Outbreak* *

| | Cases, No. |
|---|---|
| Total deliveries | 981 |
| Infants developing infection in hospital | 95 |
| Infants developing infection after discharge | 22 |
| Skin infections | 101 (86%) |
| Multiple abscesses | 6 |
| Breast abscesses | 5 |
| Pneumonia | 1 |
| Septicemia | 1 |
| Total infections | 117 (11.9%) |
| Mothers developing breast abscesses | 24 (2.4%) |

* Three-month period, June 15 to Sept. 15, 1956.

During the three-month period from June 14, 1956, through Sept. 14, 1956, a total of 981 infants were delivered and 117 were known to develop clinical staphylococcal infection (Table 1). Whereas only 2 of the infections which developed in the nursery under observation were considered serious, each of the 25 infections which developed within six weeks of birth was a medical problem. One infant's infection occurred four months after discharge. Among the clinical types of infection observed in these infants were breast abscesses, multiple abscesses, generalized pyoderma, septicemia, and staphylococcal pneumonia. Gastroenteritis and conjunctivitis were not observed as manifestations of staphylococcal infection in these infants as has been reported in other studies of staphylococcal disease of newborn infants.[11,14]

Twenty-four mothers developed breast abscesses, the usual time interval between delivery and onset of symptoms in the mothers varying from 12 to 26 days (mean, 18.3 days). The infants of five of the mothers with abscesses also had staphylococcal disease either in the nursery or at home. In at least three families in which the mother or the infant had a clinical infection, staphylococcal disease also developed in another member or members of the family. Pyoderma, furunculosis, paronychia, sinusitis, and otitis media occurred in the siblings or in the fathers.

### Epidemiological Features

The delivery rooms, the wards, and the newborn nursery, consisting of two large newborn nurseries and a suspect room,

where on the same floor. The nurseries were adjacent, with a service area between them. Attempts were made to have nursing personnel limit their work to one of the nursery rooms during a given day, but, because of the large number of infants and limited staff, often the nurses worked in both areas.

The staff of the delivery rooms, wards, and nursery were often interchanged, with a few permanent nurses forming the core of the newborn nursery staff. "Floating" personnel from other wards such as the operating rooms and medical, pediatric, or surgical ward were frequently called upon to staff the newborn nursery. No health examinations were made routinely of the nursery or delivery room staff. At the time of outbreak the load on the service was unusually high, with a daily census of about 100 infants and an average stay of five days, which strained the capacity of the hospital to provide appropriate numbers of nurses for the nursery.

Nurses donned a sterile gown upon entering the nursery and scrubbed three minutes with a detergent containing hexachlorophene, but they did not scrub between handling of individual infants. No masks were worn by the nurses. All physicians wore a sterile gown and mask when entering the nursery and washed their hands with varying degrees of vigor prior to handling the infant.

Perhaps the most unusual aspect of this outbreak is that the apparent source of disease was a chronically infected nurse who carried the "epidemic" strain. The striking correlation of her tours of duty in the nursery or delivery rooms, her episodes of clinical staphylococcal infection, and the persistence of her nasopharyngeal carrier state with the incidence of disease in the infants and mothers is shown in the Figure. The highest incidence of infections in the infants occurred during those weeks when she was on duty in the nursery. This nurse was first assigned to delivery room duty on May 1, 1956. Her medical history, taken in retrospect, indicates that she had chronic sinusitis, with intermittent nasal drainage of purulant material. An exacerbation of this disease occurred in early May. During early July she developed in succession several paronychias and pustular lesions of the perineal hair follicles and, at the height of the outbreak, required surgical drainage of a large abscess of the buttock. At the time of these later episodes her husband developed a carbuncle. From the buttock abscess and her husband's carbuncle the pathogenic strain 42B/47C/44A/52/80/81 was isolated. Both she and the physician who managed her infections were unaware of any relationship between her clinical infections and those occurring in the infants at the time.

She continued to work in the delivery rooms and nursery until Aug. 30, when her history of infection was brought out and she was taken off this duty and given antibiotic therapy, but without permanent eradication of her carrier state. Erythromycin administration for three weeks resulted in a single negative nasopharyngeal culture. Because of this negative culture she was put back on delivery room duty on Nov. 25, and infections due to the epidemic strain occurred in five infants and two mothers admitted during the next 10 days. Again the epidemic strain was isolated from her nasopharynx, but this information was not available until January. She was still working in the delivery rooms when the hexachlorophene bathing program was inaugurated. Despite the persistence of her carrier state (Figure) clinical infections no longer occurred. As soon as phage typing of her December nasopharyngeal culture was completed, revealing the epidemic strain, she was transferred permanently from the nursery and obstetric service.

Only one other member of the staff, a nursery aide, was demonstrated at any time to carry the epidemic strain. However, her carrier state was apparently temporary, since, after removal of the infected carrier, five nasopharyngeal cultures over a four-month period have not recovered the epidemic strain.

TABLE 2.—*Isolation of Epidemic Strain from Infected Infants*

| | No. |
|---|---|
| Lesions cultured | 46 |
| Coagulase-positive staphylococci | 43 |
| Typed | 30 |
| 42B/47C/44A/52/80/81 | 20 |
| Other types or nontypable | 10 |

TABLE 3.—*Characteristics of Epidemic Strain Isolated*

Bacteriophage type 42B/47C/44A/52/80/81
Coagulase-positive
α-Hemolysin, present
Antibiotic sensitivity pattern:

| Antibiotic Tested | Sensitive to | Resistant to |
|---|---|---|
| Penicillin | ---- | 100 units/ml. |
| Streptomycin | 400 μg./ml. | 200 μg./ml. |
| Tetracycline | 1.5 μg./ml. | 0.8 μg./ml. |
| Chloramphenicol | 12.5 μg./ml. | 6.3 μg./ml. |
| Erythromycin | 0.8 μg./ml. | 0.4 μg./ml. |
| Neomycin | 3.1 μg./ml. | 1.5 μg./ml. |
| Bacitracin | 0.8 units/ml. | 0.4 units/ml. |
| Polymycin | 25.0 μg./ml. | 12.5 μg./ml. |
| Novobiocin | 1.5 μg./ml. | 0.8 μg./ml. |
| Oleandomycin | 3.1 μg./ml. | 1.5 μg./ml. |

## Bacteriologic Studies

The results of phage typing of coagulase-positive staphylococci isolated from the lesions and in surveys of the staff, infants, and their mothers, are given in Tables 2 and 4. From all but three of the infants or mothers having clinical infections cultured during the course of the outbreak coagulase-positive staphylococci were isolated (Table 2).

Since bacteriophage typing was performed only upon those strains recovered after Aug. 25, data available indicating that the entire outbreak was due to a single strain are not entirely adequate. However, since a number of the infections in infants and mothers occurring up to six weeks after discharge from the hospital were due to the epidemic strain, the data are consistent with the interpretation that the epidemic strain was also responsible for the earlier cases of the outbreak. Of the 30 strains isolated from clinical infections and examined by phage typing, 20 had the "epidemic" lysis pattern. The antibiotic sensitivity pattern and other data on the strain are given in Table 3; it was penicillin-streptomycin-polymyxin-resistant, erythromycin-sensitive, and moderately chloramphenicol-sensitive.

The results of the three surveys for nasopharyngeal colonization are given in Table 4. Every member of the nursing staff, most physicians, and maintenance personnel were included in the surveys, and each infant in the nursery was included in the second and third surveys. The infants were not included in the first round of cultures. At the peak incidence of infection the first survey revealed only the two members of the staff to be harboring the epidemic strain. One of these was the nurse mentioned above; the other, the aide whose carrier state appeared to be transient. At the secondary peak the epidemic strain was isolated from a small number of babies and mothers, but only the culture from the nurse who consistently carried the strain was positive. By March, when the outbreak was quiescent, the epidemic strain was not found in the mothers, infants, or staff. As has been observed by others, the nasal carrier rate of coagulase-positive staphylococci was very high—about 80%—during the peak of the outbreak but only 39% during the period of quiescence. Since the high rate of colonization during the epidemic period cannot be accounted for by the incidence of the 42B strain, it must be assumed that factors favoring a high colonization rate by

TABLE 4.—*Results of Nasopharyngeal Culture Surveys*

| | Isolation of Coagulase-Positive Staphylococci and the Epidemic Strain | | | | | |
|---|---|---|---|---|---|---|
| | Peak of Outbreak (9/1/56) | | Second Peak (9/5/56) | | Quiescence (3/5/57) | |
| Group Cultured | Coag+ | 42B | Coag+ | 42B | Coag+ | 42B |
| Infants | -- | -- | 25/48 | 4/25 | 9/48 | 0/9 |
| Mothers | -- | -- | 4/25 | 2/4 | 13/38 | 0/13 |
| Staff | 38/48 * | 2/38 † | 16/22 | 1/16 | 20/51 | 0/20 |

* Numerator, number of nasopharyngeal cultures growing coagulase-positive staphylococci; denominator, number of persons cultured.
† Numerator, number lysed by 42B/47C/44A/52/80/81; denominator, number examined.

other strains, perhaps related to suboptimal aseptic technique or the use of dry-skin care, were also operative at the time.

## Comment

The clinical, bacteriological, and epidemiological characteristics of an outbreak of staphylococcal infection originating in a hospital nursery have been described. As in most other epidemics of staphylococcal disease reported in recent years, several conditions favoring a high incidence of infection were found to exist in the nursery, including a strain of unusual virulence, overcrowding, inexperienced personnel, and relaxed aseptic technique. However, in this particular outbreak, the prime factor in spreading and sustaining a high infection rate appears to have been the presence of a chronically infected carrier on the nursing staff. The temporal correlations established between the tours of duty of this person, with her clinical and bacteriological findings, and the incidence of infection in both the mothers and the infants are highly suggestive. Supporting her role is the finding that only one other member of the staff harbored the epidemic strain at the peak of the outbreak, and this was probably a transient colonization. Additional evidence for this source of infection is provided by the result of her return to the service.

Detailed studies of the air, dust, and blankets in the nursery area at the peak of the outbreak were not made, and the relative importance of infant-to-infant spread by these environmental mechanisms cannot be assessed. However, the principal route of seeding of the infants and their environment appears to be direct, and the exclusion of the infected carrier from the nursery resulted in cessation of the epidemic.

The relative importance of the human carrier, as compared with environmental mechanisms in the spread of nursery staphylococcal infection, is the subject of conflicting data obtained by various investigators studying outbreaks due to an identical strain. Ravenholt and LaVeck[5] and Wysham et al.[6] concluded from their studies that the blankets, air, and dust in the nursery were the principal vectors of infection by the 42B strain and that human carriers did not play a major role. No direct evidence was presented which showed that organisms in the air or on blankets directly infected the infants or were as infective as those of direct human origin. Their data agree with those of several others[3,4,15] who studied the spread of other staphylococcal strains in newborn nurseries. In contrast, the data of Shaffer and co-workers[1,8,9] indicate the significance of the chronic, as contrasted to the transient, nasal carrier in initiating and sustaining a high attack rate by an identical "epidemic" strain. The data presented here support the human vector as the mechanism of spread and suggest that such an infected person may provide a significant source of infection even while not working directly with the infants, i. e., in the delivery rooms, probably through the brief contact necessary for resuscitation, identification, and cord and eye care. The nurse in this study infected at least five infants during her second short tour of duty in the delivery room when no other carriers were present. Cross infection undoubtedly contributed to the high incidence of infection in the nursery during the peak of the epidemic, but it is probably significant that the highest weekly infection rates were observed when the carrier was working in the nursery constantly.

The presence of culturable staphylococci on linen and in the air of a nursery seems best interpreted as the end-result of having infants colonized by the epidemic strain in a nursery where "dry" care is practiced, and Staphylococcus-laden particles of vernix and epithelial debris are being constantly shed into the environment. Cross infection in the course of routine newborn care can be reduced markedly by the use of hexachlorophene bathing routinely,[8,11,13] even though nasal colonization is not prevented in this way, and posthospitalization infection is thus still a threat.[1,8] The data presented

here, supporting those already cited, suggest that the primary source or sources of staphylococcal disease affecting the neonatal infant will be found in one or more chronic, probably infected, carriers somewhere on the service. Without the identification and removal of such carriers, the usual aseptic measures could not be expected to affect the rate of nasal colonization and subsequent infection to a significant extent. Where the incidence of infection is high and the infections produced are of a more serious nature, it would appear wise to administer appropriate antibiotic therapy to all exposed infants while such carriers are identified; this was not necessary in this outbreak.[1]

The fact that a chronically infected carrier can be found working in the busy obstetrical service of a modern hospital unaware of the relationship of her difficulties to those of the nursery attests to the importance of reeducation of personnel in the principles of aseptic technique and of an administrative policy which encourages reporting illness without fear of economic loss. A policy of giving nurses found to be chronic carriers of the epidemic strain a paid vacation during which to undergo treatment should pay economic dividends over a long period of time.

## Summary

An epidemic of staphylococcal disease associated with a high rate of infection of infants and their mothers both in the hospital and after discharge has been described. The responsible Staphylococcus, the highly virulant "epidemic" strain 42B/47C/44A/52/80/81, was isolated from a majority of the lesions cultured. The outbreak appears to have been originated and sustained by a chronically infected nurse who carried the epidemic strain and worked in both the delivery room and the nursery. Control of the outbreak resulted from removal of this person from the service, without the ancillary use of antibiotics or special skin care. Although tracing an epidemic outbreak to a single infected person, such as was done here may be unusual, this experience gives appropriate emphasis to the long-established significance of human infections or chronic carrier states as the prime source of hospital staphylococcal disease.

Miss Rebecca Swanson, R.N., Mr. Henry Lee, B.A., and Dr. Eldon Berglund, cooperated in this study, and bacteriophage typing was made available through Dr. Jack Baldwin and his staff at Ohio State University, Department of Bacteriology, Columbus, Ohio.

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# Serum Oxaloacetic Transaminase Activity in Acute Rheumatic Fever

## *Values in Cases With and Without Salicylate Therapy*

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Serum glutamic oxaloacetic transaminase activity is frequently elevated in the presence of acute tissue damage[5,6] and has been found to be elevated in acute rheumatic fever.[4] Determination of this enzyme might, therefore, be helpful in the diagnosis of acute rheumatic fever and in the evaluation of the presence and severity of rheumatic carditis. In order to define more clearly the value of such determinations, patients with rheumatic fever have been studied during their acute and convalescent periods by relating serum glutamic oxaloacetic transaminase (SGOT) activity to the results of certain other laboratory tests and to the clinical status of the patient. Elevation of serum glutamic oxaloacetic transaminase has also been found during the course of salicylate administration.[7] In this study, specific attention has been given to the relationship of salicylate and cortisone therapy to the serological studies and clinical status of the patient.

### Methods

Eighteen patients selected from the pediatric and medical services of the Vanderbilt University Hospital were studied. Sixteen were children between the ages of 6 and 14 years. Eight were boys, and eight were girls. The two adults were both women, aged 25 and 28 years. All patients were hospitalized for at least a portion of the time that they were under study. All were followed by us for a minimum of six months. Each satisfied the criteria of Jones for the diagnosis of acute rheumatic fever.[3]

Of these 18 patients, 11 were thought to have active carditis when they were first admitted to the hospital. No evidence of carditis was noted in the remaining seven patients when they were first examined. Subsequently, two of these developed clinically recognizable carditis, and in a third patient a uniform opinion regarding the presence of carditis could not be reached. Thirteen of the eighteen patients received salicylates at some time during the study. The more severely ill patients were the ones treated with salicylates, and the three most severely ill also received cortisone.

Determination of SGOT activity was by the spectrophotometric method developed by Karmen et al.[6]

Serum salicylate levels were determined by the method of Brodie, Udenfriend, and Coburn.[8]

Erythrocyte sedimentation rates (ESR) were measured by the method of Wintrobe and were not corrected for hematocrit values.

C-reactive protein (CRP) determinations were made by the method of Anderson and McCarty.[8]

Antistreptolysin O (ASO) titers were determined by the method of Hodge and Swift.[6]

The term "clinical judgment" as used in the charts is based upon consideration of temperature, pulse, respiration, white blood cell count, electrocardiographic evidence of myocarditis, x-ray evidence of cardiomegaly, physical examination, and the opinions of the clinicians who examined the patients. It is independent of SGOT, CRP, ASO, and ESR values.

### Results

Charts representative of the courses of these 18 patients are presented, and the relationship of SGOT activity, ESR, CRP, ASO titer, salicylate therapy, and clinical

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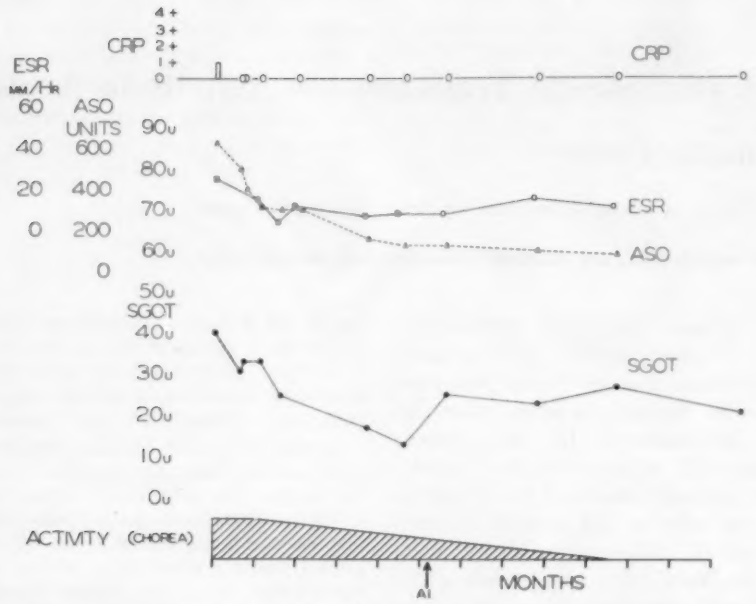


Chart 1.—Course of an 11-year-old girl with active rheumatic fever and carditis. Murmur of aortic insufficiency was first heard six months after onset of the first known attack of rheumatic fever. This patient received no salicylate treatment.

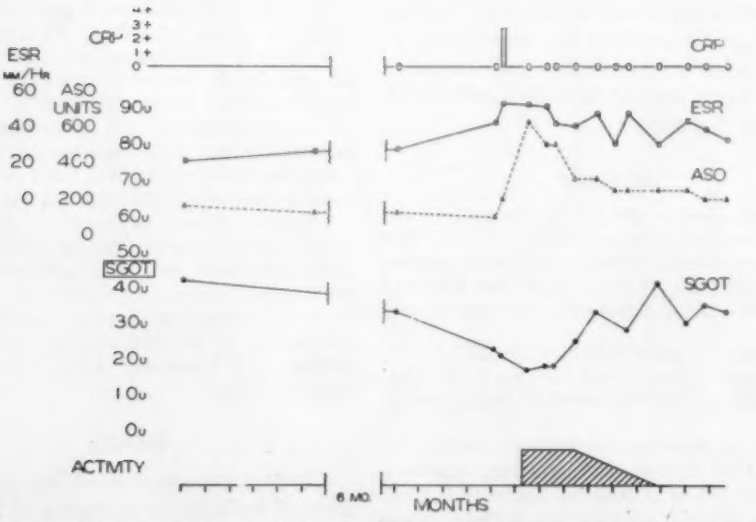


Chart 2.—Course of a 13-year-old girl with known rheumatic valvular disease who developed recurrent rheumatic fever and carditis following bacteriologically proven Group A β-hemolytic streptococcal infection. No salicylate therapy was given.

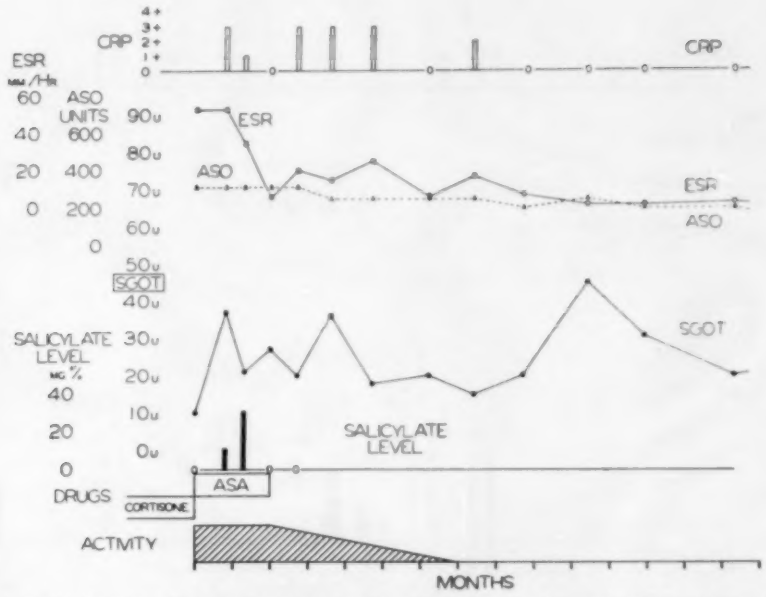


Chart 3.—Course of a 14-year-old boy with recurrent acute rheumatic fever who received cortisone and salicylates as indicated. The elevated level of SGOT late in his course occurred the week he returned to full activity.

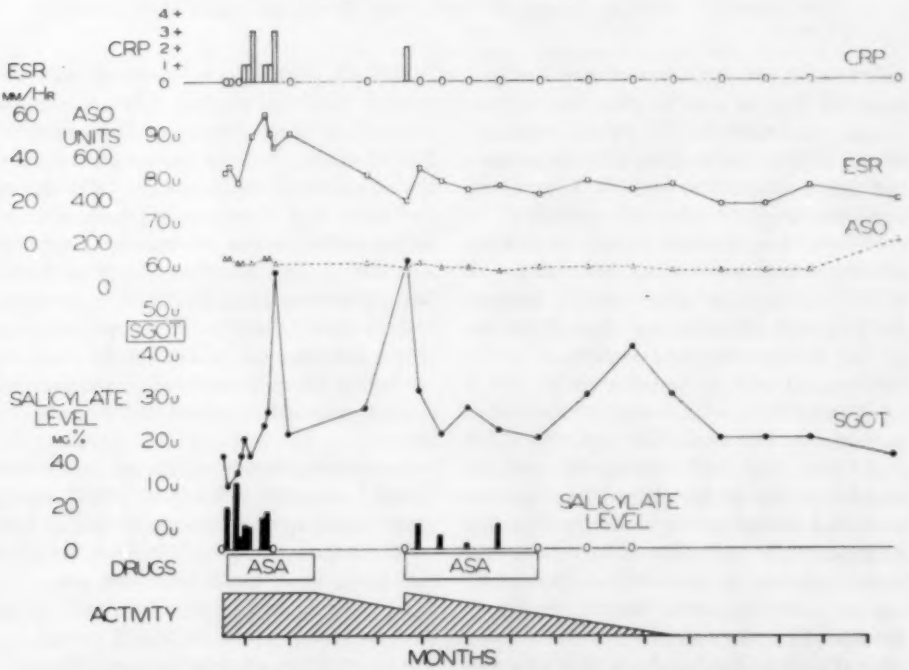


Chart 4.—Course of a 10-year-old girl with active rheumatic carditis in whom salicylate therapy was inadvertently discontinued.

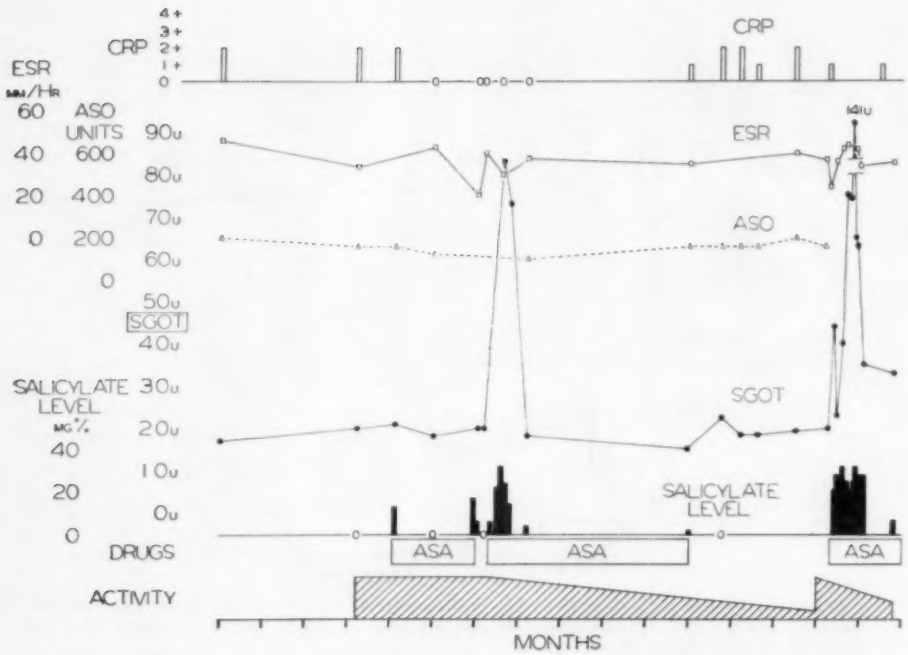


Chart 5.—Course of a 26-year-old woman with recurrent rheumatic carditis who received multiple courses of salicylate therapy. At no time was the disease thought to be completely inactive.

judgment of activity, severity, and improvement can best be seen by referring to these charts. Elevated SGOT values were obtained in 12 patients. Each of these patients had active carditis by other criteria at the time the elevated values were observed.

Of the five patients who received no salicylate treatment, three had values of SGOT activity that were initially between 20 units and 30 units and showed no rise or fall during the many months of study. One patient with an initial level of SGOT of 41 units (Chart 1) showed a very definite and steady fall in SGOT activity, CRP, ASO titer, and ESR during the first six months of the study. These four patients never had clinically recognizable carditis. The fifth patient in this group (Chart 2) showed a very definite rise in SGOT activity following a bacteriologically proven Group A $\beta$-hemolytic streptococcal infection with clinical and serologic evidence of reactivation of rheumatic carditis.

The 13 patients who received salicylate therapy exhibited marked differences in the courses of their disease as measured by SGOT activity. Three patients (Chart 3 is typical) showed no change in SGOT during the time they received acetylsalicylic acid sufficient to produce "therapeutic levels" of salicylates. The acetylsalicylic acid dosage was ¾ grain (about 50 mg.) per pound of body weight if tolerated by the patient. The single elevation of SGOT to 45 units recorded in Chart 3 occurred at the time the patient returned to school and full physical activity.

In seven patients striking but inconsistent changes occurred in levels of SGOT during administration of acetylsalicylic acid. Four of these seven patients (Charts 4 and 5 are examples) had more than one course of acetylsalicylic acid therapy, and each patient had marked elevation of SGOT values during at least one of these courses. However, each showed no change whatsoever during



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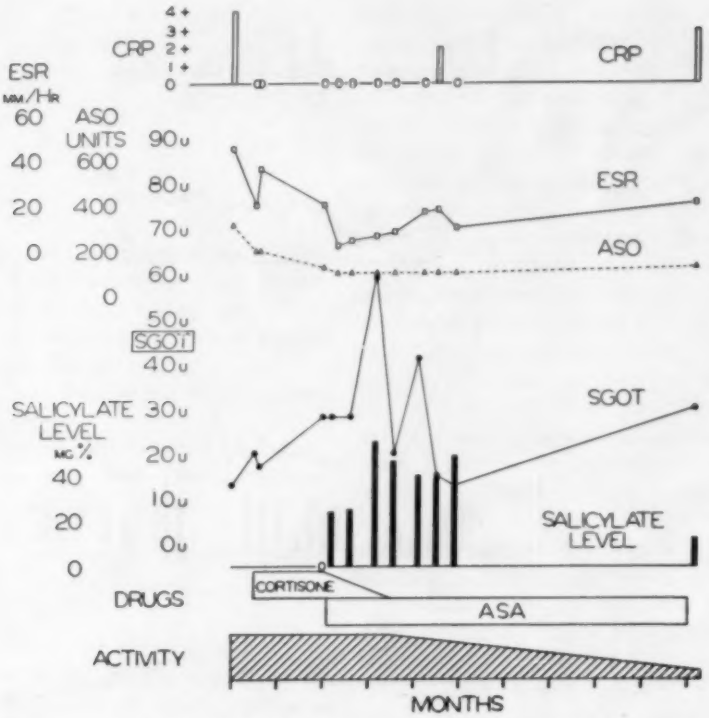


Chart 6.—Course of a 10-year-old boy with active rheumatic carditis who received both cortisone and salicylate therapy. The dosage of salicylates was constant throughout the study.

other courses of acetylsalicylic acid which were of equal dosage and productive of comparable serum salicylate levels. Three of these seven patients (as represented by Chart 6) showed an elevation of SGOT immediately after institution of salicylate therapy. These levels returned approximately to the control values during continuation of acetylsalicylic acid at identical dosage and comparable serum salicylate levels.

Two of the thirteen patients who received salicylate therapy experienced a fall in level of SGOT during combined cortisone and acetylsalicylic acid administration. Chart 7 illustrates this fall particularly well. A subsequent course of acetylsalicylic acid alone at a time when the disease was much less acute resulted in no change in the SGOT activity. A transient rise in SGOT activity occurred between the two courses of acetylsalicylic acid at a time when the patient had clinical evidence of increased activity of rheumatic fever. The remaining patient experienced a striking and constant elevation of SGOT levels while receiving acetylsalicylic acid. Acetylsalicylic acid was administered during the severest phase of the disease, which was never judged to be inactive. It is unfortunate that further study of this patient was not possible.

The more severely ill patients received salicylate therapy. These patients also had the highest and most sustained elevations of SGOT. Since elevations of SGOT have been suspected to occur secondary to salicylate therapy,[7] it was felt that particular attention should be devoted to this problem. Accordingly, control studies were performed to define the relationship of salicylates to SGOT activity. These studies are summarized in Tables 1, 2, and 3 and are described as follows.



SERUM OXALOACETIC TRANSAMINASE ACTIVITY

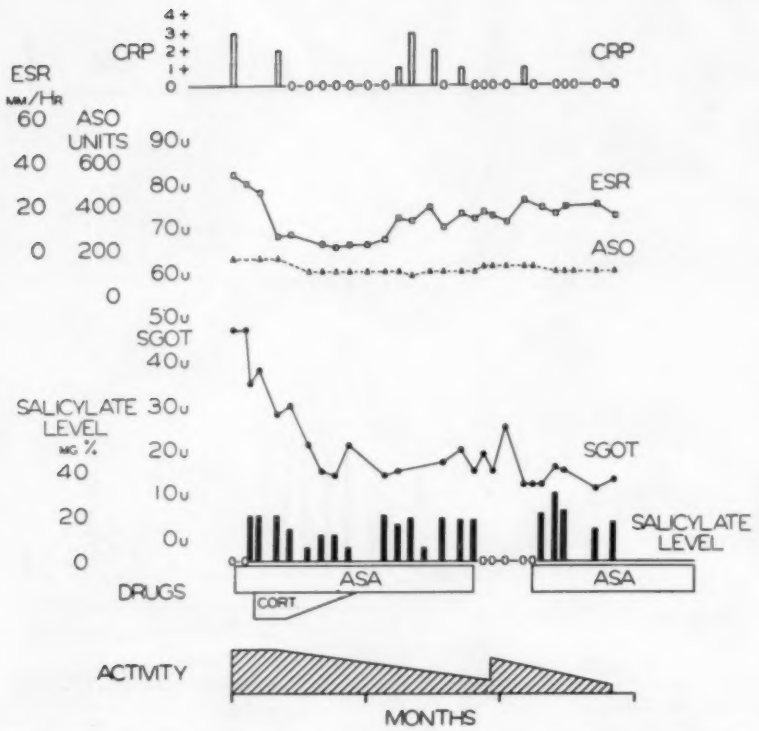


Chart 7.—Course of an 11-year-old Negro boy who had severe rheumatic carditis and who received both cortisone and salicylate therapy. Symptoms of rheumatic fever, which were completely suppressed during therapy, reappeared during the interval between courses of salicylates.

1. In vitro studies were performed by adding salicylic acid to sera of known activity. Salicylates were added so as to produce "therapeutic concentrations" of salicylate (5 to 40 mg. per 100 cc.). No change in SGOT values occurred following addition of salicylates to these sera (Table 1).

TABLE 1.—*In Vitro Studies of Effect of Varying Plasma Levels of Added Salicylate on SGOT Activity*

| Plasma Salicylate Levels, Mg./100 Cc. | SGOT Activity, Units | |
|---|---|---|
| | In Normal Serum | In Serum from Patient with Acute Myocardial Infarction |
| 0 | 20 | 75 |
| 5 | 20 | 75 |
| 10 | 22 | 77 |
| 15 | 23 | 74 |
| 20 | 19 | 75 |
| 25 | 20 | 79 |
| 30 | 21 | 78 |
| 35 | 20 | 74 |
| 40 | 19 | |

2. A normal adult man was given a large single oral dose of acetylsalicylic acid, and serum salicylate and SGOT levels were determined for the next six hours (Table 2). The SGOT values remained constant during the study. The serum salicylate level reached a peak of 16 mg. per 100 cc. in two hours and fell to 0 mg. per 100 cc. by the end of the study.

3. One adult woman with mitral stenosis, severe congestive failure, and marked hepatomegaly was given large oral doses of

TABLE 2.—*SGOT Activity in a Normal Man After Ingestion of Three Grams of Acetylsalicylic Acid*

| | SGOT, Units | Serum Salicylate Level, Mg./100 Cc. |
|---|---|---|
| Control | 25 | 0 |
| 2 hr. | 20 | 16 |
| 4 hr. | 28 | 9.4 |
| 6 hr. | 25 | 0 |

TABLE 3.—*SGOT Activity in a Thirty-Four-Year-Old Woman with Severe Congestive Failure and Inactive Rheumatic Heart Disease*

| | SGOT, Units | Serum Salicylate Level, Mg./100 Cc. |
|---|---|---|
| Control | 15 | 0 |
| 2 days | 15 | 11 |
| 4 days | ... | 17 |
| 7 days | 14 | 45 |

acetylsalicylic acid following several days of control SGOT determinations. Serum salicylate levels of about 45 mg. per 100 cc. were achieved for five days without significant change in SGOT activity (Table 3). This patient was thought not to have active rheumatic fever.

4. Two patients with marked elevations of SGOT due to liver disease showed no change in SGOT during seven days of administration of ¾ grain of acetylsalicylic acid per pound of body weight. Serum salicylate levels were not determined in these patients.

5. One 6-month-old girl entered the hospital after 3 weeks of chronic salicylate intoxication and after 48 hours of severe intoxication. The admission serum salicylate level was 56 mg. per 100 cc., and SGOT activity was 20 units. The SGOT activity was unchanged 48 hours later, when the serum salicylate level was 0 mg. per 100 cc.

6. Six patients received more than one course of acetylsalicylic acid therapy and thus served as their own "controls" to help evaluate the relationship of salicylate to SGOT activity. These patients present the most convincing data pertaining to this problem. These charts reveal that though marked elevation in SGOT activity does occur during salicylate therapy of rheumatic fever, this response is neither uniform nor constant, even with identical dosage of acetylsalicylic acid and comparable serum salicylate levels.

## Comment

These patients demonstrate that SGOT values are subject to change during the course of acute rheumatic fever. Levels above the upper limits of normal (about 40 units by this method) have been previously reported in rheumatic fever.[4] Thirteen patients in this study had elevated values by this standard. Of equal interest is the steady rise or fall of SGOT activity over a period of several weeks or months. In several cases this gradual change in SGOT activity is apparent even though a single determination might be considered normal. This is best exemplified by Chart 7, in which the first two determinations were 48 units. The next 10 determinations revealed a steady fall to about one-third of this value. In some patients the changes in SGOT values paralleled similar changes in ASO titer, ESR, and CRP and in the patients' clinical condition. However, in certain patients the changes in SGOT activity tended to lag behind similar changes in ESR, ASO titer, and CRP by several weeks. The reason for this delay in response of SGOT is not now apparent, but one can speculate that this might represent changes related to carditis in contradistinction to the other manifestations of acute rheumatic fever.

The variation of SGOT activity during salicylate administration seems to us one of the most interesting facets of this study. Several explanations come to mind, some of which can be quickly dismissed.

1. The elevation in SGOT may be a manifestation of acetylsalicylic acid toxicity. This fails to explain the elevated SGOT values in the few instances where salicylate therapy had not yet been started. The fact that subsequent trials with identical doses of acetylsalicylic acid and comparable salicylate levels often failed to reproduce these elevations weakens this hypothesis, as does the steady fall noted in Chart 7.

2. The elevation might be a manifestation of an idiosyncrasy to acetylsalicylic acid. The existence of patients who showed no response to acetylsalicylic acid on subsequent administration points away from this hypothesis.

3. The elevation may represent the effect of a combination of salicylate toxicity and hepatic congestion secondary to cardiac fail-

ure. Normal SGOT values in the patient with marked congestive failure and hepatomegaly who received large doses of acetylsalicylic acid certainly do not support this hypothesis.

4. Rheumatic fever may alter a person's response to salicylates when the disease is acute and severe. When the disease is subsiding or inactive this same person may show no change in SGOT during salicylate administration. More data would be necessary to adequately demonstrate altered metabolism as the explanation of these elevated SGOT values.

5. The elevation of SGOT may be a direct response to acute rheumatic fever and carditis. This explanation is certainly a possibility, but the very frequent elevation in SGOT immediately after acetylsalicylic acid was started suggests that salicylates are in some way involved in this temporary elevation of SGOT activity.

## Summary and Conclusions

Eighteen patients with acute rheumatic fever were studied over long periods with serial determinations of serum glutamic oxaloacetic transaminase (SGOT) activity, C-reactive protein (CRP), antistreptolysin O titer (ASO), and erythrocyte sedimentation rate (ESR). Detailed charts are included which show the relationship between these serologic studies.

SGOT activity was elevated in some patients with acute rheumatic fever. These elevations were inconstant, however, and equally ill patients sometimes showed no elevation.

Elevated values of SGOT occurred only in the patients who had active rheumatic carditis. However, rheumatic carditis was frequently not accompanied by elevation in SGOT.

A single determination of SGOT activity was of little value in diagnosing acute rheumatic fever or in following the course of the disease. Some values that were not above the "upper limit of normal" were demonstrated to be significantly elevated when serial determinations were performed.

A rise and fall in SGOT values was often well correlated with ESR, CRP, and ASO titer determinations as well as with the clinical status of the patient.

Administration of acetylsalicylic acid did not affect SGOT activity in the absence of active rheumatic carditis.

The effect of salicylates on SGOT activity in the presence of active rheumatic carditis was uncertain, and inconstant results were obtained in several patients.

Mrs. Frances Womack, M.A., gave technical assistance in the determination of ASO titers and CRP reactions.

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# Infection Following Splenectomy in Infants and Children

*A Review of the Experience at Duke Hospital in Infants and Children During a Twenty-Two-Year Period (1933-1954)*

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The incidence of sepsis following splenectomy, particularly in infants, is a subject of current interest. King and Shumacher [1] in 1952 reported the occurrence of meningitis in four of five infants splenectomized under 6 months of age for congenital hemolytic anemia. Smith et al.[2] in 1956 reported severe infections after splenectomy in 14, or 28%, of 50 infants and children. Gruber et al.[3] reported overwhelming bacteremia with death in a premature infant 14 days after splenectomy for thrombocytopenic pupura. Robinson [4] reported pneumococcal meningitis in a 5-month-old infant six weeks after splenectomy for congenital hemolytic anemia. In a review of 107 splenectomies in infants and children Gofstein and Gellis [5] found severe infections after operation in 4 patients. They eliminated from their series those patients whose primary disease was a factor in increased susceptibility to infection.

On the other hand, there have been many reports of successful splenectomies without untoward sequelae in infants and children.[6-11] Walter and Chaffin [12] reported 37 splenectomies in infants and children with congenital hemolytic anemia. Ten patients were less than 7 months of age, and no severe infections were encountered. Follow-ups ranged from 10 months to 13 years.

In 1954, in a review of the case histories of five children with a peculiar syndrome characterized by eczema, thrombocytopenic purpura, and draining ears, an increased incidence of severe infections was noted in these children following splenectomy.[13] A review of the Duke Hospital splenectomy cases in infants and children was then undertaken.

Fifty-eight patients 13 years of age and younger were splenectomized at Duke Hospital during the years 1933 through 1954. Of this number, 12 patients were not included in the series because of a follow-up period of less than six months. These patients either died during this time of causes other than sepsis or failed to return for examination after discharge or to answer the questionnaire. One of these patients was followed for seven weeks; one, for six weeks; two, for four weeks, and the rest, for two weeks or less. Patients dying of sepsis during the first six-month period are included in the study. Forty-six patients remain, and of this number seven patients were considered to have had serious infections following splenectomy (Table 1).

Sixteen splenectomies were done for idiopathic thrombocytopenic purpura. Four patients developed severe infections after operation. Three of these patients had a syndrome consisting of eczema, thrombocytopenic purpura, and draining ears and have been reported in detail elsewhere.[13] Their ages at operation were 25 months, 19 months, and 16 months. One patient died two and a half months postoperatively with septicemia and adrenal hemorrhage (confirmed at autopsy), in another hospital. One patient developed pneumococcic meningitis three months postoperatively from

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TABLE 1.—*Patients Classified According to Disease, Showing the Number of Patients Under One and Two Years of Age and the Number of Patients Developing Infections*

| Diagnosis | Total No. of Cases | No. Followed 6 Mo.* | No. Under 1 Yr. of Age | No. Under 2 Yr. of Age | No. Who Developed Severe Infections |
|---|---|---|---|---|---|
| Idiopathic thrombocytopenic purpura | 19 | 16 | 2 | 3 | 4 |
| Congenital hemolytic anemia | 12 | 11 | 2 | 3 | 0 |
| Anemia and sicklemia | 7 | 6 | 1 | 2 | 1 |
| Portal hypertension | 10 | 6 | 1 | 1 | 1 |
| Ruptured spleen | 3 | 2 | | 0 | 0 |
| Acquired hemolytic anemia | 2 | 1 | | 0 | 0 |
| Cooley's anemia | 1 | 1 | | 0 | 0 |
| Adrenal carcinoma | 1 | | | | |
| Hodgkin's disease | 1 | 1 | | 0 | 0 |
| Hypoplastic anemia | 1 | 1 | | 1 | 0 |
| Letterer-Siwe disease | 1 | 1 | 1 | 1 | 1 |
| | 58 | 46 | 7 | 11 | 7 |

* Patients dying of sepsis during first six-month period are included.

which he recovered, only to die later with pneumonia. One patient developed meningitis of unknown type eight months after operation from which he recovered and died later with bleeding and marasmus. The fourth patient, 10 years of age at operation, had had no history of increased susceptibility to infection before operation. She developed ecthyma two months after operation and rheumatoid arthritis six months after operation and again four years later. She had pneumococcic meningitis three and a half years postoperatively, pyelonephritis four years postoperatively, and staphylococcal septicemia four and a half years postoperatively. At last contact she was well 11 years after operation. The remaining 12 patients had no significant difficulty.

Eleven splenectomies were done for congenital hemolytic anemia, and two patients were under one year of age. There were no serious infections in this group.

Six splenectomies were done in patients with anemia and sicklemia. One patient, aged 10½ months at operation, developed meningitis of unknown type 3 months postoperatively and pneumococcal meningitis 10 months postoperatively. This was the only patient in this group under 2 years of age. The remaining five patients were not considered to have serious infections. However, one patient had repeated episodes of pharyngitis after operation, pneumonia three years after operation, and acute purulent otitis media one and three years after operation. One other patient was seen in the emergency room 11 years after operation with signs of meningeal irritation. He was referred to another hospital, and I have no further follow-up.

Six patients had portal hypertension. There was only one patient under 2 years of age (10 months). He developed lobar pneumonia from which he recovered one month after operation. Two weeks later he developed fever and ascites and died with the presumptive diagnosis of peritonitis. No autopsy was performed. In the remaining five patients no serious infections were encountered.

One patient aged 10 months with Letterer-Siwe disease died eight months postoperatively with pneumonia. Her basic disease was still present.

There were two cases of ruptured spleen, one case of acquired hemolytic anemia, one case of Cooley's anemia, one case of Hodgkin's disease, and one case of hypoplastic anemia. All did well postoperatively. One patient was under one year of age.

## Comment

Of 46 patients 13 years of age and under splenectomized at Duke Hospital during the years 1933 through 1954, there were 7 who developed severe infections after operation. Of these patients who developed severe infections postoperatively, five were boys and two were girls. Five of the seven were

TABLE 2.—*Patients Classified According to Age, with the Number of Patients Who Developed Infections in Each Group and the Type of Infection Encountered*

| Age at Operation, Yr. | Total No. of Cases | No. Followed 6 Mo. | No. with Serious Infections | Diagnosis (Basic Disease) | Type of Infection Acquired | Time After Operation Infection Acquired |
|---|---|---|---|---|---|---|
| Over 6 | 30 | 25 | 1 | I. T. P.* | Chronic echthyma | 2 mo. |
| | | | | | Rheumatoid arthritis | 6 mo. |
| | | | | | Meningitis (pneumococcal) | 3 ½ yr. |
| | | | | | Acute pyelonephritis | 4 yr. |
| | | | | | Septicemia (staphylococcal) | 4 ½ yr. |
| 3–6 | 14 | 10 | 0 | | | |
| 1–3 | 7 | 4 | 1 | E. P. D.† | Septicemia & adrenal hemorrhage (fatal) | 2 ½ mo. |
| Under 1 | 7 | 7 | 5 | Portal hypertension | Lobar pneumonia | 1 mo. |
| | | | | | Peritonitis (fatal) | 6 wk. |
| | | | | Letterer-Siwe | Pneumonia (fatal) | 8 mo. |
| | | | | Anemia & sicklemia | Meningitis (type undetermined) | 3 mo. |
| | | | | | Meningitis (pneumococcal) | 10 mo. |
| | | | | E. P. D. | Meningitis (pneumococcal) | 3 mo. |
| | | | | E. P. D. | Meningitis (type undetermined) (fatal) | 8 mo. |

* Idiopathic thrombocytopenic purpura.
† Triad of eczema, purpura, and draining ears.

under 1 year of age at operation, one was 14 months of age, and one was 10 years of age. There appears to be, in our series, a definite relationship between age and susceptibility to infection following splenectomy. Of seven patients under one year of age at the time of splenectomy, five developed severe infections after operation (Table 2).

Of the seven patients who had severe infections postoperatively, five had diseases which are associated with an increased susceptibility to infection. Three had the eczema, purpura, and draining ears triad. One had portal hypertension, and one had Letterer-Siwe disease. Although, with this small series of cases, it is impossible to draw any definite conclusions concerning the type of patient who will develop severe infections after splenectomy, one should be cautious in recommending splenectomy in patients with the eczema, thrombocytopenia, and otitis triad and in patients with diseases usually associated with an increased susceptibility to infection. After operation in these children any illness, however minor, should be regarded as an emergency—to be observed assiduously and be given antibiotic therapy as soon as possible if infection is suspected. Perhaps the effect of splenectomy on resistance to infections is sufficient, when added to the basic susceptibility in these patients, to produce a marked change in the incidence of severe complications. In other splenectomized persons, less basically affected, this change in incidence may become significant only in a larger series than is presented here.

The effect of splenectomy on resistance to infection is not understood. Further studies should be done in patients to determine what effect, if any, removal of the spleen has on the immune mechanism. The quantitative measurement of specific antibody response before and after splenectomy would be helpful.

## Summary

Fifty-eight cases of splenectomy in infants and children from Duke Hospital are reviewed. Of the 46 patients with adequate follow-up, 7 had serious infections after operation. Five of these patients were under one year of age, and in five patients the basic disease was one which is associated with an increased susceptibility to infection. Splenectomy is particularly hazardous in patients who, as a result of their basic disease, show decreased resistance to infection before operation.

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# A New Reflex in Young Infants

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Juanico and Pérez del Pulgar Marx [1] described in 1955 a new reflex in newborn infants, hereafter called the Pérez reflex, which seems to have aroused little attention. We have been able to confirm many but not all observations of the Spanish authors.

The reflex is elicited with the baby lying in prone position on a hard surface, e. g., an examination table or mattress, or held face down on the examiner's hand. Using moderate pressure, the examiner runs his index finger or thumb along the spine from the pelvis upward to the neck.

In response to this stimulus, Juanico and Pérez list the following reactions:

(1) flexion of the lower extremities
(2) lordosis of the spine, with elevation of the pelvis
(3) flexion of the upper extremities, with elevation of the head
(4) strong cry, leading in many cases to glottic spasm with apnea and occasional cyanosis
(5) urination
(6) relaxation and protrusion of the anal sphincter, occasionally with expulsion of feces and gas
(7) generalized hypertonia for a few seconds after the reflex is fully developed.

After a short refractory period of a few seconds to one minute the reflex can again be elicited.

According to the Spanish authors, this reflex is present on the first day of life, is most intense during the first week, persists for several weeks, and then gradually disappears. Premature infants show a less intense response than do full-term babies. Osseous or peripheral nerve lesions in the extremities lead to asymmetric responses. In severe central nervous lesions, the reflex may be absent in early infancy, or it may persist in older infants as a sign of immaturity of the central nervous system.

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## Material and Observations

In cooperation with Dr. Marguerite J. Gates, we studied this reflex in a total of 123 infants, including 79 full-term newborn infants (Sloane Hospital nursery) during the first week of life; 20 premature infants (premature nursery, Babies Hospital, New York), aged 4 to 46 days, with an average age of 19.6 days, weighing between 985 and 2100 gm.; 24 full-term infants (private practice) who were examined at various intervals between birth and 4 months of age. With the exception of one Mongoloid, all infants were regarded as normal.

In contrast to Juanico and Pérez, we preferred to elicit the reflex on the infant held face down on the examiner's hand (Fig. 1). This position permits the observation of free motor responses unhindered by the baby's prone position. A moderate stimulus usually suffices. The younger the infant the less stimulus is required to elicit a positive response. If the first stimulus is unsuccessful, a somewhat stronger stimulus has to be applied, which generally leads to a positive reflex. The infant should be relaxed and quiet when the reflex is elicited. Repeated positive responses are usually followed by a short refractory period, after

Fig. 1.—The Pérez reflex is elicited by a cephalad stimulus along the spine.

Fig. 2.—Motor responses of the Pérez reflex.

which a new response can be obtained by the same stimulus.

Running the finger along the spine caudad instead of cephalad is—if at all—considerably less effective. Premature infants show a weaker response than full-term infants.

All infants showed a positive reflex during the first month of life. The frequency of the various reflex components, however, varied greatly, in the following order:

| | Per Cent |
|---|---|
| Flexed arms | 99 |
| Cry | 98 |
| Flexed legs | 97 |
| Lordosis | 85 |
| Elevated head | 78 |
| Anal dilatation | 19 |
| Urination | 1 |
| Others | 0 |

It appears that urination occurs rarely and by chance and is not a component of the reflex. Anal dilatation was observed in about one-fifth of the cases but may be secondary to the prolonged cry and temporary anoxia rather than a part of the reflex.

Most constant are flexion of the arms and legs and a vigorous, prolonged cry (Fig. 2), in only one instance accompanied by a glottic spasm and cyanosis. The lack of one or another component of the reflex in an individual child can not be regarded as a constant phenomenon peculiar to the infant. Repetition of the reflex or a stronger stimulus may elicit a previously missing component. Elevation of the head, for instance, may be lacking if the stimulating finger is not carried entirely up to the cervical spine and may appear at a second trial with a more complete stimulus. The same is true for the lordosis of the spine.

The reflex becomes weaker during the second month of life but is rarely absent. During the third month the reflex gradually disappears, persisting beyond this time only in rare instances. Our longitudinal observations are limited but indicate that the time of disappearance shows wide variations around the third month of life.

The Moro reflex was tested in all infants examined for the Pérez reflex. Both reflexes were positive in all babies during their first month of life. However, it is obvious that the Moro and the Pérez are different reflexes. In the Moro reflex there are abduction and extension of the extremities followed by adduction and flexion ("embracing") mainly of the arms, while in the Pérez reflex there is only flexion of the extremities. Lordosis and elevation of the head and pelvis are constituents of the Pérez but not of the Moro reflex. The penetrating cry so characteristic of the Pérez reflex is not a necessary component of the Moro reflex and is not mentioned in Moro's [2] original description. With gradually increasing stimuli we were able to elicit a full Moro reflex without a cry in most infants; this is not possible with the Pérez reflex. The reflexes do not disappear simultaneously. In a number of instances, in the third month of life, the Moro reflex was found positive and the Pérez, negative or vice versa in the same child.

My observations on brain-damaged infants were too limited (only 10 infants could be tested during the past one and one-half years) to permit a conclusion as to the diagnostic and prognostic value of the Pérez reflex. In all cases in which the Moro reflex could not be elicited during the first month of life, the Pérez reflex was absent too. It was my impression and that of Dr. Sidney Carter [3] that the two reflexes have a similar significance and that the ab-

sence of the Pérez reflex during the first month or its persistence beyond the third month is suggestive of central nervous system pathology. A representative example is a 4-day-old infant with kernicterus due to Rh incompatibility; both Moro and Pérez reflexes were absent. Another child with kernicterus, severe rigidity, and myoclonic jerks had positive Pérez and Moro reflexes at the age of 7 months.

On the other hand, presence of both reflexes during the first trimester does not rule out brain damage. An example is a premature infant, weighing 1570 gm. at birth, with cytomegalic inclusion disease, hydrocephalus, and slight generalized muscle rigidity. This baby showed on the 54th day of life a positive Moro reflex, with coarse tremor of the extremities; the Pérez reflex was positive also but was modified by tremor and incomplete flexion of the extremities; no retroflexion of the head could be elicited. An atypical reflex may be of significance. The compatibility of a positive Pérez reflex with severe brain damage in a young infant was demonstrated by a 3-hour-old anencephalic baby who showed positive Pérez and Moro reflexes.

## Comment

We could find no description of the reflex earlier than that of Pérez[1] previously cited. Closest to it is Galant's[4] "spine reflex" published as an inaugural dissertation in Basel in 1917. Stroking the skin near the spine and parallel to it produces a lateral arching of the infant's body, the concavity of the arch directed to the side of the stimulus. In addition to this, Peiper[5] observed extension of the lower extremity at knee and hip on the same side and flexion on the other, also retroflexion of the pelvis and occasional turning of the head to the side of the stimulus. Galant observed this reflex during the first few months of life and interpreted it as a protective reflex (*Sicherungsreflex*). The motor responses of the Galant reflex seem to be different from those of the Pérez reflex.

Like the Moro reflex, the Pérez reflex may be regarded as an expression of immaturity of the central nervous system in young infants due to insufficient myelinization of the pyramidal tract or to the absence of cerebral inhibition or to both. Both reflexes disappear around the age of 3 months even if both do not disappear simultaneously.

Moro[2] interpreted his reflex as an atavistic phenomenon, an expression of an "embrace instinct" characteristic of those mammal sucklings which are carried at their mother's breast. In Moro's opinion, the embracing movements elicited by a startling stimulus probably represent a reflex search for maternal protection.

The motor responses of the Pérez reflex are distinctly different and would not serve the same purpose. The dorsiflexion of spine, head, and pelvis as well as the flexion of the extremities would rather detach a suckling clinging to his mother from a protective attachment. These movements somewhat resemble those of a runner at the start of a race, the flexed extremities favoring a forceful start (*Sprungbereitschaft* of Magnus[6]). If we assume the Pérez reflex to be a flight reflex, the shrill cry—an essential component of the Pérez but not of the Moro reflex—could be regarded as appropriate; while expressing fright it simultaneously startles the attacker and gives the attacked a better chance to get away. The Pérez reflex can be elicited only at the spine and better by a stroke cephalad than caudad. Animals of prey usually attack their victims over the spine, aiming at the neck. It may well be that the Pérez reflex is an atavistic fright-flight reflex.

We tried to find out whether the Pérez reflex is present in other primates. A young gorilla at the zoo of Columbus, Ohio, showed a negative response on the 55th day of life.[7] The proper time for testing the reflex had probably been missed, since the motor behavior of a gorilla is well advanced as compared with that of human infants. A 12-day-old chimpanzee at the

Yerkes Laboratories of Primate Biology,[8] Emory University, showed extension of legs and toes but no vocalization and no response of arms, head, and back. Three baby monkeys at the Department of Biology,[9] The University of Chicago, showed dorsiflexion of the back with head and pelvis coming up but no vocalization. The extremities were flexed already when the stimulus started and remained that way. These animal observations, being few in number, were inconclusive.

## Summary

A new reflex in young infants, first described by Juanico and Pérez del Pulgar Marx, has been evaluated in 123 infants; many but not all observations of the Spanish authors could be confirmed.

The reflex is elicited along the spine and consists essentially of a vigorous cry, flexion of the extremities, and lordosis of the spine with elevation of the head.

In normal infants this reflex is always present during the first month of life and almost always during the second month, and it gradually disappears during the third month of life. Premature infants show a weaker response than full-term infants.

The reflex is distinctly different from the Moro reflex but may have a similar significance, expressing an immaturity of the central nervous system in young infants. Both reflexes disappear around the third month but not always simultaneously.

The reflex is interpreted as an atavistic fright-flight response to a cephalad stimulus along the spine.

In a limited number of observations on brain-damaged children it appeared that absence of the Pérez reflex during the first month or its persistence beyond the third month are suggestive of central nervous system pathology. On the other hand, presence of the Pérez reflex during the first trimester does not seem to rule out brain damage.

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# Prolonged Obstructive Jaundice in Infancy

## *V. The Genetic Components in Neonatal Hepatitis*

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During the past few years increasing attention has been directed toward a group of infants with prolonged obstructive jaundice not associated with erythroblastosis fetalis or biliary atresia. This syndrome is characterized by onset of jaundice during the first weeks of life, acholic stools, dark urine, and moderate hepatomegaly and splenomegaly. Laboratory studies on these infants show their urine to contain bile and their stools to be free of both bile and urobilinogen, the flocculation tests of liver function being usually negative. The one-minute and total serum bilirubin are, however, always elevated and show either a slowly falling or variable trend. Histological examination of the liver reveals focal or widespread hepatocellular degeneration, often with the formation of multinucleated liver cells or liver "giant cells." Follow-up studies have revealed that about 60% of these infants recover without sequelae, some develop cirrhosis despite treatment, and a small group die as a result of either cirrhosis or the complications of surgery. It has been felt that this condition may result from several different causes, none of which is fully understood, and, for this reason, the disease state has been variously termed neonatal hepatitis, infantile hepatitis, "giant-cell" hepatitis, or merely the "inspissated bile syndrome of unknown etiology." [1-9]

Although various workers [1,3,4,6] have postulated that this disease represents a viral hepatitis transmitted from the mother to the infant in utero, no convincing evidence for any specific agent has been presented. The virus for infectious hepatitis appears to have been ruled out by the complete absence of jaundice and liver involvement in several groups of infants born of mothers who were known to have had infectious hepatitis during pregnancy.[10,11] Repeated efforts have been made to reproduce the disease by passage of serum and stools from such infants and their mothers in egg embryos, conventional tissue cultures, and special tissue cultures with human embryonic material, with no success. Boggs and his co-workers [12] have administered serum from three mothers and their five affected children and bacteria-free stool filtrates from two mothers and two infants through the oral route to groups of volunteers. None of the volunteers either developed hepatitis or showed abnormalities of liver function.

Weller and his co-workers [13] have recently recovered inclusion-cell virus from three infants with neonatal hepatitis. However, similar efforts have been unsuccessful in other such infants. This would suggest that inclusion-cell virus may be the cause of a number of cases of neonatal hepatitis, but the etiology of the majority of such cases is still unknown at the present time.

In view of the fact that several instances of neonatal hepatitis are sometimes seen in

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the same family, it appeared worth while to make an analysis of a possible hereditary component in the pathogenesis of this disease. In doing this, we fully realize that we are dealing with a relatively limited number of families with a condition which may have more than one etiology.

## Materials and Methods

The present study includes a total of 59 families with one or more offspring affected with neonatal hepatitis. Forty-seven of these families have been reported in a previous communication from The Children's Medical Center in Boston.[4] Nine additional families have been added from the files of The Children's Memorial Hospital in Chicago. The remaining three families were abstracted from the literature where adequate data are available for this type of analysis.[6,7] It should be emphasized that the other communications on neonatal hepatitis[1,5,8] were excluded only because the information presented was inadequate.

The criteria used for the diagnosis of neonatal hepatitis have been outlined in previous communications.[2,4] In each instance erythroblastosis fetalis was effectively ruled out by means of blood-grouping tests.

All except three of the families have been resurveyed, and the material has been analyzed from the following viewpoints: (1) familial incidence, (2) the parents, (3) the siblings, (4) sex incidence, (5) other genetic considerations, (6) birth order, and (7) outcome of affected cases.

## Results

The results of the study are summarized in Table 1. The data were analyzed as follows.

1. *Familial Incidence.*—First, it was necessary to establish that the incidence of neonatal hepatitis is in fact greater in these families than in the general population. In the present study, there was a total of 120 children in 59 families. If one excludes the first, or index, case in each family, there were 61 siblings. Of these, 11 developed neonatal hepatitis and 50 were well and free of jaundice during early infancy. The number of affected siblings could well be even greater if the gene expression is incomplete. For instance, infants with no evidence of icterus clinically have been found to show changes characteristic of neonatal hepatitis at postmortem examination.

As controls, we selected 33 families with infants with atresia of the bile ducts proven by surgical exploration. This group seemed most appropriate for comparison, since they also developed jaundice early in infancy and frequently their condition cannot be differentiated from neonatal hepatitis on clinical or laboratory grounds. In these families there was a total of 73 children. After excluding the index cases, there were 40 siblings. Of these, none developed jaundice during infancy.

With use of these figures, the difference between the two groups is statistically highly significant ($\chi^2$ [1 degree of freedom] = 7.92; $P<0.01$).

2. *The Parents.*—Having shown that the incidence of neonatal hepatitis within families is increased, one must next decide whether this occurs on a genetic basis. The first approach is to see if the trait is transmitted as a Mendelian dominant.

If neonatal hepatitis is transmitted as a dominant, one would expect half of the parents to be similarly affected. Even assuming that the penetrance is incomplete, one would still expect some of the fathers and mothers to have developed jaundice either in early infancy or even later in life. Whether this was so was asked of all of the mothers and some of the fathers, and we can note only two instances when this might have been a factor. In one, the father was reported to have been jaundiced during early infancy but had made an uneventful recovery. In the other, the mother developed jaundice briefly during pregnancy but had subsequently recovered.

On the basis of the above evidence, there is little to suggest that neonatal hepatitis is transmitted as a Mendelian dominant.

3. *The Siblings.*—We can next analyze the data for a recessive mode of inheritance. With both parents normal, one would expect one out of four offspring to be affected with the disease.

TABLE 1.—*Summary of Data*

| Family | Order of Birth * | | | | | Total Offspring | No. Unaffected | No. Affected | Sex of Affected | | | Outcome of Affected | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | | | | M | F | Unknown | Recovered | Sequelae | Unknown |
| 1 | A † | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 2 | A † | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 3 | A ‡ | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 4 | A | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 5 | A | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 6 | A | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 7 | A | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 8 | A ‡ | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 9 | A ‡ | — | — | — | — | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 10 | A † | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 11 | A | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 12 | A | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 13 | A ‡ | — | — | — | — | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 14 | A ‡ | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 15 | A | — | — | — | — | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 16 | A ‡ | — | — | — | — | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 17 | A ‡ | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 18 | A ‡ | — | — | — | — | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| 19 | A | — | — | — | — | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 20 | A | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 21 | A ‡ | — | — | — | — | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 22 | N | A ‡ | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 23 | A ‡ | *A* ‡ | — | — | — | 2 | 0 | 2 | 0 | 2 | 0 | 0 | 2 | 0 |
| 24 | N | A | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 25 | A | N | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 26 | N | A ‡ | — | — | — | 2 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 27 | A ‡ | N | — | — | — | 2 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 28 | N | A ‡ | — | — | — | 2 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 29 | N | A ‡ | — | — | — | 2 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 30 | N | A † | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 31 | N † | A ‡ | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 32 | *A* † | A | — | — | — | 2 | 0 | 2 | 2 | 0 | 0 | 1 | 0 | 1 |
| 33 | N | A | — | — | — | 2 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 34 | N | A ‡ | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 35 | N | A ‡ | — | — | — | 2 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| 36 | N | A ‡ | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 37 | N | A | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 38 | A ‡ | A ‡ | — | — | — | 2 | 0 | 2 | 1 | 0 | 1 | 1 | 1 | 0 |
| 39 | A ‡ | A ‡ | — | — | — | 2 | 0 | 2 | 0 | 0 | 2 | 0 | 2 | 0 |
| 40 | N | A ‡ | — | — | — | 2 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 41 | N | A | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 42 | N | A † | — | — | — | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 43 | A ‡ | N | N | — | — | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 44 | N | N | A ‡ | — | — | 3 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| 45 | N | N | A ‡ | — | — | 3 | 2 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 46 | N | N | A ‡ | — | — | 3 | 2 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 47 | A | N | N | — | — | 3 | 2 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 48 | N | N | A † | — | — | 3 | 2 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 49 | N | A † | N | — | — | 3 | 2 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| 50 | N | N | A ‡ | — | — | 3 | 2 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| 51 | N | N | A ‡ | — | — | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 52 | A ‡ | N | N | — | — | 3 | 2 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 53 | N | N | A ‡ | — | — | 3 | 2 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| 54 | *A* ‡ | N | *A* ‡ | — | — | 3 | 1 | 2 | 0 | 0 | 2 | 0 | 2 | 0 |
| 55 | A ‡ | A ‡ | *A* ‡ | N | — | 4 | 1 | 3 | 2 | 1 | 0 | 3 | 0 | 0 |
| 56 | N | N | N | A ‡ | — | 4 | 3 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 57 | N | N | N | A ‡ | — | 4 | 3 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 58 | N | *A* ‡ | *A* ‡ | *A* ‡ | — | 4 | 1 | 3 | 1 | 1 | 1 | 0 | 3 | 0 |
| 59 | *A* ‡ | N | N | *A* ‡ | *A* ‡ | 5 | 2 | 3 | 2 | 1 | 0 | 0 | 3 | 0 |
| | | | | | | 120 | 50 | 70 | 41 | 23 | 6 | 41 | 27 | 2 |

* A, affected; N, normal. *A*, proband.
† Surgically explored.
‡ Liver biopsy or autopsy.

The proportion of affected offspring, computed by Weinberg's sib method,[14] with use of the observed ascertainment, is $0.260 \pm 0.076$, as shown in Table 2. Since the difference between the expected and observed number of affected persons is well within the variance, the data are consistent with a recessive mode of inheritance.

4. *Sex Incidence.*—Next, we turn to the question of whether the condition is sex-linked. In the present series, sex of the affected child was not known in six instances. Of the remaining infants, there were 41 boys and 23 girls. Assuming random distribution, there would be 53 boys among each 100 infants at this age. The difference between the expected and observed ratios is not statistically significant ($\chi^2$ [1 degree of freedom] $= 1.94$; $P$ 0.10-0.20).

TABLE 2.—*Proportion of Affected Offspring*

| $s$ | $r$ | $a$ | $n_{s,r,a}$ | $n_{s,r,a}(s-r)$ | $n_{s,r,a}(r-1)$ |
|---|---|---|---|---|---|
| 2 | 1 | 1 | 17 | 17 | 0 |
| | 2 | 1 | 4 | 0 | 4 |
| 3 | 1 | 1 | 11 | 22 | 0 |
| | 2 | 2 | 1 | 2 | 2 |
| 4 | 1 | 1 | 2 | 6 | 0 |
| | 3 | 1 | 1 | 1 | 2 |
| | 3 | 3 | 1 | 3 | 6 |
| 5 | 3 | 3 | 1 | 6 | 6 |
| | | | | 57 | 20 |

$P=\frac{20}{77}=0.260 \pm 0.076$

$s$=number of offspring in family including the proband(s)
$r$=number of affected offspring in each family
$a$=number of probands per family
$n_{s,r,a}$=number of families of size $s$, with $r$ affected and $a$ ascertained independently

This would suggest that neonatal hepatitis is transmitted as an autosomal recessive trait.

5. *Other Considerations.*—Several other factors should be taken into consideration in such an analysis: A. Twins. There was only one pair of twins in the entire series. It was not known whether they were monozygotic or dizygotic. Both twins developed jaundice during early infancy. B. Consanguinity. As far as is known, there were no instances of cousin marriages in any of the 59 families studied. C. Other relatives. Neonatal hepatitis has not been known to occur among direct or collateral relatives in any of the families studied.

These observations, although not particularly helpful in offering further information on the mode of inheritance of neonatal hepatitis, nevertheless serve to show that there is nothing to contradict the concept that the disease is transmitted by a recessive gene.

6. Birth Order.—In 21 families the infant with neonatal hepatitis was the only child. In 24 families the infant with neonatal hepatitis was the last child, although they had had one or more previous unaffected children. One woman gave birth to twins, both of whom were jaundiced.

In the remaining 13 families, six women gave birth to a total of nine unaffected children after an initial infant had developed neonatal hepatitis. Three women had "mixed" pregnancies. One gave birth to a normal infant and then subsequently an affected infant, another to two affected infants and then a normal infant, and another to two normal and then to two affected infants, all after having had an affected child. Finally, three women each gave birth to an additional affected infant and one woman gave birth to two affected infants after having had an infant with neonatal hepatitis.

This would suggest a random distribution of affected and normal infants in these families.

7. *Outcome of Affected Cases.*—Finally, it is necessary to determine whether the sex of the infant, the birth order, or the familial pattern in any way alters the prognosis of the affected infant. For this purpose, all the affected children were divided into two groups: (*a*) recovered—those who on follow-up were free of jaundice and completely well—and (*b*) with sequelae—those who have subsequently developed cirrhosis of the liver or have died of complications from the disease process. Except for two instances, the ultimate outcome of each child was successfully traced. It was found that 41 infants recovered and 27 developed sequelae or died, a ratio which is similar to ratios previously reported.[4]

Considering first the outcome on the basis of the infant's sex, it was found that among the boys 26 recovered and 14 developed sequelae, while among the girls 14 recovered and 8 developed sequelae. The difference is not significant statistically ($\chi^2$ [1 degree of freedom]$<0.10$).

The influence of birth order is shown in Table 3. The differences are not statistically significant ($\chi^2$ [2 degrees of freedom]$=$ 1.8; $P$ 0.30-0.50).

The familial pattern is shown in Table 4. Among the families with a single affected

TABLE 3.—*Influence of Birth Order*

| Pregnancy No. | Total No. | Recovered | Sequelae |
|---|---|---|---|
| 1 | 32 | 21 | 11 |
| 2 | 22 | 15 | 7 |
| 3, 4, 5 | 14 | 5 | 9 |
| | 68 | 41 | 27 |

TABLE 4.—*Familial Pattern*

| Affected Children in Family, No. | Total No. | Recovered | Sequelae |
|---|---|---|---|
| 1 | 50 | 36 | 14 |
| 2 | 9 | 2 | 7 |
| 3 | 9 | 3 | 6 |
| | 68 | 41 | 27 |

child, 36 children recovered and 14 developed sequelae. Among those with two affected children, two recovered and seven developed sequelae. Finally, among those with three affected children, three recovered and six developed sequelae. Although the numbers in the last two groups are small, it does appear that the incidence of complications is greater in those families with multiple cases.

## Comment

It is necessary to emphasize that the etiology of neonatal hepatitis is unknown at the present time. Although the present analysis shows a good genetic fit for an autosomal recessive mode of inheritance, this does not indicate that neonatal hepatitis is actually a hereditary condition. However, we must add this new dimension to our thinking on the subject.

First, let us consider inclusion-cell virus as an etiologic agent. It is generally agreed that this virus manifests itself in the newborn infant in various ways. In the severest form the disease is generalized and fulminating, so that the infant either is stillborn or dies shortly after birth. At postmortem examination inclusion cells are seen in major organs in the body. In the milder forms one may see only the salivary glands involved, or the inclusion cells may appear in the urine, presumably as a result of shedding of tubular epithelium. Although it is conceivable that inclusion cells may be seen in the liver without affecting the other organs, this probably occurs only in rare instances. Moreover, one seldom sees inclusion cells in the kidney in patients with neonatal hepatitis, and the recovery of inclusion-cell virus by Weller et al.[13] may well explain only the occasional case.

Next, the virus of infectious hepatitis (IH) should be considered as a possible etiologic agent. Again, the evidence is not convincing at the present time, because (1) infants born of mothers with known infectious hepatitis do not develop jaundice and liver disease[10,11]; (2) none of the mothers of patients with neonatal hepatitis have shown abnormal liver-function tests either during or between pregnancies[4] (it is difficult to regard a mother as having infectious hepatitis without either jaundice or at least some changes in liver function), and (3) it is generally believed that persons develop antibodies against this virus rapidly after exposure, and this immunity remains permanent.[15,16] This would tend to prevent such a mother from producing a second child with neonatal hepatitis.

Third, the virus of homologous serum hepatitis (SH) should be considered as a possible etiologic agent. Stokes et al.[17] and Neefe et al.[18] have presented evidence that certain persons may be "silent carriers" of the SH virus, often remaining carriers for many years. Since these studies have considerable bearing on the possible etiology of neonatal hepatitis, we should examine the data in greater detail. Stokes presents the history of three such "carriers." The first carrier is known to have transmitted hepatitis to at least 4 out of 12 recipients of his blood over a three-year period. His blood was also administered to four male volunteers, one of whom developed hepatitis. Liver-function tests in this carrier frequently were abnormal, and a liver biopsy showed periportal fibrosis. The second carrier was the mother of an infant who developed hepatitis at the age of 2 months. Although liver-function tests of the mother were normal, volunteers given serum from her and her infant developed hepatitis. The third carrier was known to have transmitted hepatitis to at least four recipients of his blood, including one volunteer. He had abnormal liver-function tests. The carriers described by Neefe et al.[18] presented essentially the same findings. (In a group of

22 carriers about half showed abnormal or equivocal liver-function tests.)

What is the evidence that neonatal hepatitis is transmitted in utero by mothers who are "silent carriers" of the SH virus? The question might be considered in three different ways. First, in what way do the mothers resemble these "silent carriers"? Scott and his co-workers [6] have reported finding the cephalin-cholesterol flocculation test positive in one such mother. However, in careful studies on a considerable number of the mothers, we have never found any evidence of abnormal liver-function tests, whereas this seems to be a common finding among the "silent carriers." Second, with the exception of the first carrier described by Stokes et al., virus appears to have been present each time they were used as blood donors and, with a single exception, when their serum was given to volunteers. This would imply that, once present, the virus carrier state was maintained permanently, or at least for a period of years. In this series, six women gave birth to nine unaffected children after the initial affected child, a finding which is not consistent with a permanent viremia. Moreover, the findings of Stokes and Neefe suggest that this virus does not appear to be a transient one which comes and goes depending on the health and environmental factors in the host. At least, there is no evidence to indicate that the viremia can come and go in these persons. In the present study, we have three women who had "mixed" pregnancies, giving birth to normal children between affected ones.

Recently, Burnet [19] has postulated that serum hepatitis may be a variant of infectious hepatitis, with two special qualities: A. Its antigenicity is decreased so that no antibodies against the IH virus are produced, and it is not influenced significantly by IH antibodies. At the present time, it is not yet clear why some persons have effective antibodies against SH virus and others do not. B. In some cases the SH virus infects the fetus in utero, and these persons may become life-long carriers of the virus in a fashion analogous to Traub's mice with L. C. M. virus infection.

Thus, although the silent carrier of the SH virus is an attractive possibility, it requires confirmation by means of virus-transmission studies. The same arguments can hold for the transmission of some other, hitherto undescribed, viral agent.

Finally, Smetana and Johnson [20] have proposed on pathological grounds that neonatal hepatitis may represent a developmental defect of liver cells resulting in aplasia of bile capillaries and malformation of liver cells. They propose that all of these changes take place in utero and that the jaundice makes its appearance after birth because of greatly augmented physiological demands on the liver at this time. If this is actually so, one could speculate that these morphological changes are the result of some insult to the liver early in embryonic life which is in some way genetically determined. Most probably, this process has been completed by the time the infant is born and the basic disease process does not progress. Instead, we observe clinically only the damage done to the liver. In the milder cases the undamaged cells proliferate and complete recovery takes place. In the severer cases the damage is irreversible, and cirrhosis and hepatic failure result.

The present discussion does not yield the etiology of neonatal hepatitis. It may still be that the disease results from more than one cause or even from multiple causes in the person. We could well be dealing with several different hereditary diseases, as has been shown recently in glycogen-storage disease and adrenal hyperplasia. However, we hope that it emphasizes the imperfection of each of the theories advanced regarding the etiology. We feel that a genetic interpretation may prove to be of value for future workers in the field.

## Summary

A total of 59 families with one or more cases of neonatal hepatitis have been analyzed from the genetic viewpoint.

After excluding the index cases, there were 11 affected and 50 normal siblings in these families. In a similar survey there were no affected and 40 normal siblings in a group of 33 families with atresia of the bile ducts studied as controls. The difference is highly significant.

Analysis by the Weinberg sib method showed the trait to be consistent with an autosomal recessive mode of inheritance.

There were six women who gave birth to nine normal children after the affected child. In three other families, women gave birth to affected, then normal, and then, again, affected children.

While the present survey does not effectively rule out the possibility of an intrauterine factor as responsible for neonatal hepatitis, a genetic etiology should also be considered.

Miss June Samuels assisted in locating some of the families.

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# Use of a Single-Lead ECG in the Detection of Congenital Heart Disease

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This study was undertaken in an attempt to investigate the hypothesis that a single-lead electrocardiogram taken from the right precordium ($V_3R$) on a mass survey basis could detect a large proportion of operable congenital heart defects associated with right ventricular hypertrophy (RVH). These defects would include atrial septal defect, pulmonic stenosis, tetralogy of Fallot, "atypical" patent ductus arteriosus, and some varieties of ventricular septal defect.

The $V_3R$ lead was chosen as the single lead for study in accord with the findings of Sokolow and Lyon [8] and of Katz et al.,[2] who have demonstrated that right precordial leads seem to be the most sensitive indicators of RVH. Single leads have been used previously on ECG mass surveys.[4] The single lead used has generally been standard Lead I and has been shown to be a rather poor indicator of heart disease when used as a mass survey device.

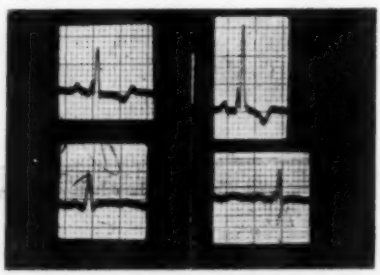
Witham and Coggins [10] have developed a 4-lead electrocardiogram which compares very favorably with the complete 12-lead electrocardiogram as regards sensitivity and accuracy of diagnosis. However, since any mass screening program must necessarily separate all its subjects into "abnormal," "borderline," and "normal" groups, it was believed that confusion would be minimized if the screening device were kept as simple as possible. Therefore, the single lead ($V_3R$) was selected.

The criteria for abnormality (indicating RVH) of the $V_3R$ lead were as follows: (1) ratio of R wave to S wave in $V_3R$ greater than 1, (2) prolongation of the ventricular activation time in $V_3R$ to 0.04 second or longer, and (3) presence of a prominent "crista" pattern.

If two of the criteria were present in the same tracing, the $V_3R$ tracing was judged "abnormal"; if only one criterion was present, the tracing was judged to be "borderline"; all the rest were "normal" (Figs. 1, 2, and 3).

A word of explanation about the "crista" pattern: The crista pattern (Fig. 2, Tracings *A*, *D*, and *E*) is an rSr′ complex observed normally in right precordial leads.

Fig. 1.—Typical abnormal $V_3R$ electrocardiogram tracings. Both of the following criteria are present: (1) ventricular activation time of 0.04 second or longer; (2) ratio of R wave to S wave greater than 1.



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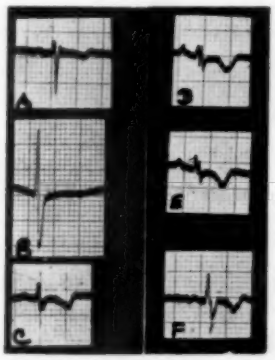

Fig. 2.—Typical borderline $V_5R$ electrocardiogram tracings. One of the following criteria is present: (1) R/S ratio greater than 1; (2) ventricular activation time 0.04 second or longer; (3) a prominent "crista" pattern.

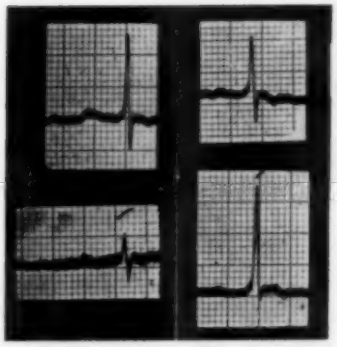

Fig. 3.—Typical normal $V_5R$ electrocardiogram tracings. Both of the following criteria are present: (1) R/S ratio less than 1; (2) ventricular activation time less than 0.04 second.

Increased prominence of the r' wave may be the earliest sign of right ventricular outflow tract hypertrophy.

## Method of Study

The study was carried on over a period of two years in Durango, Colo., a community of 12,000 population with an active interest in school and community health programs. The $V_5R$-lead tracings were obtained by the use of portable Sanborn & Beck-Lee direct-writer electrocardiographs. School nurses were instructed by physicians on the standard technique of obtaining the $V_5R$ lead. The skin was cleansed with alcohol sponges, and the electrodes were attached directly. No electrode paste was used. This technique provided an adequately legible tracing and significantly reduced the time involved in taking the tracing. School nurses were aided by volunteer members of the school P. T. A., who took charge of dressing and undressing the children. It was found that $V_5R$ leads could be obtained at a rate of about 240 children per six-hour school day by this technique.

A physical examination was performed subsequently to or simultaneously with the $V_5R$-lead tracing. This examination consisted of the following procedures: inspection and palpation of the chest; evaluation of neck veins; cardiac auscultation in the upright, supine, and left lateral positions; palpation of the femoral pulses, and determination of blood pressure in the arms and legs when indicated. These examinations were performed by six doctors who had had previous pediatric cardiac experience. The physicians worked in teams to facilitate frequent consultations.

Although 1846 $V_5R$-lead tracings were obtained, only 1617 children were available for the physical examinations. The 229 children who failed to receive follow-up physical examinations are an indication of the migratory nature of Durango inhabitants. The 1617 children from whom were obtained both the $V_5R$-lead tracing and the physical examination constitute about 75% to 80% of the elementary-school population over the two-year study period. The distribution by age, sex, and follow-up status of all children who had $V_5R$-lead tracings taken is presented in Table 1.

## Results

On the basis of physical examination alone, the six primary screeners selected 47

TABLE 1.—*Distribution by Age, Sex, and Follow-Up Status*

| Age, Yr. | Group Followed Up | | | | Group Not Followed Up | | | | Total of Columns 1 & 5 |
|---|---|---|---|---|---|---|---|---|---|
| | Total (1) | Male (2) | Female (3) | Unknown (4) | Total (5) | Male (6) | Female (7) | Unknown (1) | |
| 6 or less | 315 | 173 | 142 | 0 | 27 | 17 | 9 | 1 | 342 |
| 7 | 359 | 189 | 170 | 0 | 46 | 25 | 21 | 0 | 405 |
| 8 | 238 | 119 | 139 | 0 | 49 | 26 | 23 | 0 | 307 |
| 9 | 277 | 157 | 120 | 0 | 50 | 24 | 26 | 0 | 327 |
| 10 | 186 | 98 | 88 | 0 | 29 | 18 | 11 | 0 | 215 |
| 11 | 145 | 80 | 65 | 0 | 14 | 6 | 8 | 0 | 159 |
| 12 or more | 77 | 43 | 34 | 0 | 10 | 7 | 3 | 0 | 87 |
| Unknown | 0 | 0 | 0 | 0 | 4 | 1 | 3 | 0 | 4 |
| Total | 1,617 | 859 | 758 | 0 | 229 | 124 | 104 | 1 | 1,846 |

TABLE 2.—*Distribution by Interpretation, Follow-Up Status, and Clinical Diagnosis*

| $V_3R$-Pattern Interpretation | Total Tracings Taken | Number Followed Up | Clinical Diagnoses of Cases Followed Up | | | |
|---|---|---|---|---|---|---|
| | | | Congenital Heart Disease with RVH | Other Types of Congenital Heart Disease | Rheumatic Heart Disease | No Heart Disease |
| Abnormal | 19 | 19 | 5 | 0 | 0 | 14 |
| Borderline | 173 | 163 | 0 | 1 | 0 | 162 |
| Normal | 1,654 | 1,435 | 1 | 2 | 12 * | 1,420 |
| Total | 1,846 | 1,617 | 6 | 3 | 12 * | 1,596 |

* Includes four cases of past rheumatic fever who had no apparent valvular heart disease at the time of study.

children as either having heart disease or needing further evaluation before heart disease could be ruled out. These children were checked by a consultant pediatric cardiologist, who verified 17 cases of organic heart disease (not including one case of Wolff-Parkinson-White syndrome). The condition of the remaining 30 children was deemed within normal limits.

The $V_3R$-lead tracings were evaluated entirely separately and without knowledge of the results of physical examination. The distribution of the children as to $V_3R$-pattern interpretation, follow-up status, and subsequent clinical diagnosis is presented in Table 2.

It is to be noted that 19 "abnormal" $V_3R$-lead tracings produced a yield of five children who on complete evaluation had congenital heart disease associated with RVH. The case with RVH and a "normal" $V_3R$-lead tracing was a case of tetralogy of Fallot and will be discussed later in the paper. The five cases of congenital heart disease with RVH and "abnormal" $V_3R$ tracings consisted of three cases of atrial septal defects, one case of pulmonic stenosis, and one case of tetralogy of Fallot; four of these five cases had been previously unknown. Of the "other types" (Column 5 in Table 2) the case with the "borderline" $V_3R$ tracing was a case of ventricular septal defect without RVH and the two cases with "normal" $V_3R$ tracings consisted of a case of patent ductus arteriosus and one of ventricular septal defect, both without RVH.

One must consider the specificity and sensitivity of this test in the detection of congenital heart disease with RVH. From a study of Table 2 it is evident that, with 14 false-positives in the abnormal group, the specificity of this test is 5/19, or 26%. It is also evident that, with one false-negative in the normal group, the sensitivity of this test is 5/6, or 83%. If one wishes to calculate the efficiency of such a test, the product of the specificity and the sensitivity yields an index of efficiency which, in this instance, is 21.6%.

In an attempt to increase the efficiency of the screening test, the crista pattern could probably be omitted as a criterion of abnormality. This is appropriate because it was observed that none of the cases of organic heart disease in this series had had a prominent crista (rSr′) pattern. This would result in the redistribution of the results of this study shown in Table 3.

After this revision, the specificity is 5/14, or 35.7%; the sensitivity is 5/6, or 83%, and the index of efficiency is 29.6%. There were no further revisions of criteria that

TABLE 3.—*Revised Results of Study*

| $V_3R$ Interpretation | Original Total | Crista Patterns | Revised Total | Clinical Diagnosis | | | |
|---|---|---|---|---|---|---|---|
| | | | | Congenital Heart Disease | | Rheumatic Heart Disease | No Heart Disease |
| | | | | RVH | Other Types | | |
| Abnormal | 19 | 5 | 14 | 5 | 0 | 0 | 9 |
| Borderline | 163 | 43 | 120 | 0 | 1 | 0 | 119 |
| Normal | 1,435 | 56 | 1,483 | 1 | 2 | 12 | 1,468 |
| Total | 1,617 | 109 | 1,617 | 6 | 3 | 12 | 1,596 |

TABLE 4.—*Relation of Functional Murmurs to Sex*

| | Age, Yr. | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 or Less | | 7 | | 8 | | 9 | | 10 | | 11 | | 12 or more | | All Ages | | Total |
| | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | |
| Functional murmur present | 56 | 24 | 55 | 40 | 52 | 29 | 61 | 42 | 33 | 24 | 27 | 15 | 12 | 8 | 298 | 182 | 480 |
| Functional murmur absent | 115 | 118 | 134 | 127 | 65 | 106 | 92 | 76 | 64 | 62 | 51 | 49 | 31 | 26 | 552 | 564 | 1,116 |
| Total | 173 | 142 | 189 | 167 | 117 | 135 | 153 | 118 | 97 | 86 | 78 | 64 | 43 | 34 | 850 | 746 | 1,596 |

could be successfully made in the direction of increasing the efficiency of this test.

An interesting sidelight to the main question was the occurrence of "functional" or innocent murmurs in this group. Of the 1596 children without heart disease, 480, or 30.1%, had functional murmurs of one type or another. No attempt was made to differentiate the different types of functional murmurs, because of possible differences between the criteria of the six primary screeners. There was no statistical correlation between functional heart murmurs and age, type of $V_3R$ tracing, presence of crista pattern, or heart rate. However, there was an interesting correlation between the presence of a functional murmur and the sex of the child.

Table 4 reveals that, even though there were more boys than girls in this study, the relatively greater prevalence of functional heart murmurs in boys is of definite significance ($t=4.7$; $P<0.01$). Although the necessary information which would give a basis for statistical validation was not recorded, several of the screeners observed that functional murmurs seemed to be noticeably more frequent in the schools in the low-income districts. This suggested that perhaps nutritional anemia might be a factor in the etiology of functional murmurs in this locale. However, no proof for this latter suggestion was obtained.

Remarks should be made regarding the prevalence of heart disease in this group. Included in the group, for this purpose only, are two children with organic heart disease who are known to have intentionally avoided the screening procedure. One girl with proven atrial septal defect excused herself from the original screening procedure on the grounds that she had just had a complete electrocardiogram made the previous week, and one boy with known rheumatic mitral insufficiency "skipped school" every day for two weeks because of his fear of doctors and the possibility that he might have been sent to the hospital. One should not attempt to extrapolate the figures to the entire group, since there is no knowledge of the other children who were not screened.

The total population for the prevalence estimate is 1619 children, aged 6 to 13 years. Of these, 10 children have congenital heart disease and 9 have valvular rheumatic heart disease. The prevalence of all heart disease in this group at this time is 1.17%. The prevalence of congenital heart disease is 0.62%, and that of valvular rheumatic heart disease is 0.55%. This estimate of prevalence of heart disease among school children is higher than others reported to date. Although the position of this study is vulnerable on the grounds of population selection, it is believed that this prevalence is valid for this population and at least partially reflects the thoroughness of the screening procedure.

This estimate of prevalence can be made more meaningful by thinking of it as applied to a hypothetical town of about 20,000 population. In such a town with about 5000 children in the elementary schools, the physicians in the town might be called upon, in one way or another, to diagnose as many as 31 cases of congenital heart disease and 28 cases of valvular rheumatic heart disease in any two-year period. These figures will vary slightly in different locales, but they indicate that every physician who is seeing and treating children, even if just for routine school or summer camp physical ex-

aminations, should be prepared to identify the abnormal heart sounds and murmurs associated with congenital or rheumatic heart disease.

It is of interest that 4 of the 10 cases of congenital heart disease in Durango were atrial septal defects. This is a lesion which is often difficult or impossible to recognize in preschool children and can remain undiagnosed and asymptomatic until early adulthood.

## Comment

To be effective and to justify the expense, a screening program for a relatively uncommon type of disease should be as efficient as possible. As anyone who has worked with the electrocardiogram realizes, interpretation of patterns is often fraught with uncertainty. This study revealed that the abnormal ECG tracings are completely overlapped by the normal range of pattern appearance. However, the probability of finding cases of the type sought in the "abnormal" group as contrasted with the "normal" groups is so great that this method can be used as a screening device with considerable justification.

In a study such as this, one might consider whether or not it is necessary to examine children in both "abnormal" and "borderline" ECG categories. This study seems to indicate that only persons in the "abnormal" category need to be completely examined subsequently (Table 3). The main concern in this study was the one false-negative result. There is some doubt about the recording technique that resulted in missing this case; however, the case is included for purposes of statistical validity and frank evaluation.

This screening procedure or a modification of it should be tested further in an effort to substantiate or disprove these findings. The fact that this many cases of organic heart disease were discovered is of considerable significance to the community of Durango. In addition, one may roughly compare this screening method with another method now in use for detecting another disease.

TABLE 5.—*Comparison of Two Screening Tests*

| Screening Tests | No. Screened | Total No. of Positive Tests (Suspected Disease) | No. with Active Disease |
|---|---|---|---|
| $V_3R$ for RVH (in children) | 1,000 | 12 | 3 |
| Chest x-ray for TB (in adults) | 1,000 | 10 | 1 |

From Table 5 one may see that use of the $V_3R$ lead will be more productive in the detection of RVH among school children than will the chest x-ray in the detection of tuberculosis among adults in an average community.

## Conclusion

With use of the $V_3R$ lead as a screening device for RVH, five cases of surgically correctable congenital heart disease associated with RVH were discovered. In addition, during the investigation, 12 other cases of organic heart disease were discovered.

Among 1619 Durango elementary-school children the prevalence of all organic heart disease was 1.17%, with the prevalence of congenital heart disease being 0.62% and that of rheumatic heart disease being 0.55%.

Among the children without organic heart disease in this group, the prevalence of "functional" heart murmurs was 30.1%.

The following institutions aided in this study: Colorado Heart Association; Heart Disease Control Program of the U. S. Public Health Service; Colorado State Department of Public Health; Public and Parochial Schools of Durango, Colo.; Durango Heart Association; Colorado University School of Medicine; San Juan Basin Medical Society; San Juan Basin Health Unit.

Heart Disease Control Program, 1422 Grant St. (3).

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# Use of Combined Hormone and Mechlorethamine (Nitrogen Mustard) Therapy in Lipoid Nephrosis

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The effectiveness of adrenal steroids and corticotropin (ACTH) in reversing the signs and chemical abnormalities associated with lipoid nephrosis is well known. In the majority of cases in which these agents are used, diuresis, cessation of albuminuria, and return to normality of the various serum constituents are observed. On the other hand, the effect of hormone therapy is short-lived, and many cases so treated will have one or more recurrences of the disease. It is doubtful whether use of hormone only at times when marked edema is present significantly alters the natural history of the disease [1]; the fatality rate for patients treated in this manner is approximately 25% to 35%.[2,3]

In recent years an effort has been made to prevent recurrences by giving prolonged therapy with adrenal steroid or corticotropin while the disease is in remission. The patient is given small doses of hormone, usually steroid, daily, or, more frequently, large daily doses are given for three consecutive days each week in the so-called intermittent regimen.[4,5] There is evidence that treatment designed in this manner to suppress recurrences of the disease reduces the fatality rate.[2]

Despite this advance, difficulties arise. Children with active disease are rather frequently encountered who are refractory to hormone therapy in that, despite administration of the agent in high doses over a long period, diuresis and reversal of the chemical abnormalities do not occur. Intermittent therapy also has its disadvantages. It results in the development of hyperadrenocorticism, with its potential dangers, and in the severe nephrotic it may not be successful in preventing exacerbations of the disease unless the dose of hormone is excessive. Further, institution of intermittent therapy shortly after the first diuresis has been deemed important,[5] since second or third episodes may be refractory to hormone treatment. Adherence to this rule results in needless treatment of a certain fraction of the patients who would not have a recurrence in the absence of such therapy.

The form of therapy to be described, employing a combination of hormone and mechlorethamine hydrochloride (nitrogen mustard; methyl-bis-[$\beta$-chloroethyl] amine hydrochloride), offers an alternative method of handling the patient with "pure" lipoid nephrosis.* Experience with such combina-

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* The term "pure" lipoid nephrosis has been used to denote a disease characterized by the changes typical of the nephrotic syndrome which is capable of remission with return to normality of the serum constituents, cessation of albuminuria, and loss of edema. The remission may be spontaneous or induced by hormone therapy, of brief or of long duration. The patients reported in detail in this paper all demonstrated, when first studied, the ability to have remissions. A few had hypertension and elevation of the concentration of blood urea nitrogen either before or during hormone therapy. These abnormalities have not excluded them from the category of pure nephrosis. The results of a limited experience with combined hormone-mechlorethamine therapy in patients with "chronic" nephrosis, characterized by disease of long standing in which albuminuria is always present and unresponsive to hormone therapy, are also briefly discussed.

tions in small series of patients has been described previously by Lestina, Freeman, and Wilson [6] and by Taylor.[7] The present study extends these observations and indicates that by administering mechlorethamine during the last days of a course of corticotropin, or of steroid followed by corticotropin, two advantages are gained: (1) A remission occurs in a very high percentage of the cases, even in the patient refractory to hormone therapy, and (2), under certain conditions of therapy, the resultant remission will be a long one. The first of these advantages makes combined therapy valuable in the patient with severe nephrosis as an adjunct to forms of therapy commonly in use. The second advantage, production of a long remission, is the chief concern of the present report. The study indicates that, by making use of the long-remission aspect, combined therapy can be used exclusively with success in the management of the nephrotic without recourse to intermittent regimens. There is room for improvement, however, in that somewhat over half the patients have had to have two or more courses of combined treatment before a remission with a prospect of being permanent was achieved. There is a possibility that, with further experience with different combinations of the two agents, the results can be improved.

## Method of Treatment and Its Evaluation

As originally used by Startzman and Mercer,[8] the combined-therapy regimen consisted of a 10-day course of aqueous corticotropin, 40 mg. daily administered intramuscularly, with administration on Days 6, 7, 8, and 9 of 0.1 mg. of mechlorethamine per kilogram intravenously. It was their experience that this regimen produced a remission in a very high percentage of the cases. In the present series of patients, this schedule has been altered, chiefly in the direction of increasing the duration of treatment with corticotropin before mechlorethamine is given and on some occasions of substituting adrenal steroids for part of the corticotropin course. In addition, the corticotropin has been given in the form of the gel in a dose usually of 80 mg. daily. In some very small children the dose has been 60 mg. daily, and in one 10-year-old boy (Case 9) the dose was 100 mg. daily. To allow evaluation of the combined therapy, intermittent therapy with steroid or corticotropin has not been given while the child is in remission after combined therapy.

While the patient is receiving corticotropin or steroid, potassium chloride, 1 to 1.5 gm. daily; calcium lactate, 1 to 2 gm. daily, and a prophylactic antibiotic have been given. No dietary restriction of salt has been imposed. During long courses of hormone treatment, aluminum hydroxide gel U. S. P. (Amphogel) has been used occasionally to forestall complications resulting from increased gastric acidity.

Mechlorethamine was administered intravenously, with the usual precautions. Usually the total dose of 0.4 mg. per kilogram was divided into four equal doses of 0.1 mg. per kilogram and was given on four successive days. However, in patients in whom venipuncture was difficult the total dose was given in three injections over a four-day period. In all cases the interval between courses of mechlorethamine has been two months or more. Before a repeat course is given, blood cell counts are obtained to make sure that no hematological abnormality exists as a residual from the previous course. In no case has such an abnormality been found.

In general, every effort has been made to keep the children out of the hospital. New patients have been hospitalized until diuresis has occurred. At the time of discharge the parents were instructed in testing the urine for albumin, either by the sulfosalicylic acid test or by the colorimetric bromophenol blue method,† and were shown how to grade the result. The records kept each day by the parents, both of the results of the test and of the medication given, furnished a large portion of the data for the present paper. When the parents noted albuminuria, the physician was consulted and the course of treatment was planned. Albuminuria alone was considered an indication for treatment. Steroid and corticotropin were given in the home, the latter by the Visiting Nurse Association; the children were hospitalized only to receive mechlorethamine.

Since therapy was started when albuminuria first appeared, recurrences usually did not progress to edema except in patients who became refractory to hormone therapy. In evaluation of the results of treatment, the presence of albuminuria has been taken as indicating activity of the disease and its absence, as indicating remission.

† Materials for these tests (Bumintest Reagent Tablets and Albustix) were in large part furnished by the Ames Company, Elkhart, Ind.

## Results

The two chief concerns in the therapy of the nephrotic child are, first, to induce a remission of the disease and, second, to prevent the development of subsequent recurrences. With use of combined therapy, there has been no problem in inducing a remission; all patients with so-called pure nephrosis have responded with diuresis and, except for one, cessation of albuminuria coincident with addition of mechlorethamine to hormone therapy. Thus the main emphasis in the following discussion of individual cases is on the problem of inducing a long remission.

At the outset, to clarify the discussion of the results, it should be pointed out that several factors and conditions are probably involved in inducing a long remission with combined therapy. One of these is the duration of hormone therapy prior to institution of mechlorethamine treatment. The relationship between duration of therapy and duration of remission was discovered as experience with the combined regimen was gained. Initially mechlorethamine was used only for patients who had a severe form of the disease in that they were either refractory to hormone treatment or had frequent exacerbations of their disease. Good results in these patients in the form of relatively long remissions prompted its use in patients with infrequent recurrences or who had recently developed the disease. In these, the results were not impressive; all had diuresis, but the duration of the remission was not long. In review of the data, the only factor which could be related to the length of the remission after combined therapy was the duration of hormone therapy prior to starting mechlorethamine therapy. All who had a long period of pretreatment had relatively long remissions. Similar results have been obtained in patients treated subsequently. In the following discussion, therefore, duration of the pre-mechlorethamine-treatment period has been emphasized. Since, in many instances, hormone was not given daily in this period, the duration of pretreatment has been expressed as the number of days hormone was administered in the 30-day period (arbitrarily selected) immediately prior to the beginning of mechlorethamine injection. This method of expression appears justified in view of the fact that discontinuous therapy did not discernably alter the results. It should be noted, however, that it has been deemed important to give hormone each day for the six-day period immediately preceding, and for the four-day period during, mechlorethamine administration. The single instance in which hormone was not given continuously just prior to mechlorethamine treatment will be noted.

In addition to the duration of pretreatment, another factor which may well affect the duration of the remission is the type of hormone used in pretreatment. In the present series two types of pretreatment have been used, corticotropin alone and steroid followed by corticotropin. Use of steroid alone is a third possibility, which has not been tried. The results indicate that both types of pretreatment have been effective; the data are not sufficient to demonstrate a definite superiority of one over the other.

Other factors which have not been evaluated are the optimal dosage of hormone and the time of stopping hormone therapy after completion of mechlorethamine injections. In the present series corticotropin has always been given the day after the last mechlorethamine injection and then discontinued. The status of the disease at the time mechlorethamine is given, whether active with albuminuria present or in remission, appears not to be a factor determining the effectiveness of combined therapy in inducing a long remission.

Twelve patients with pure lipoid nephrosis, followed for periods ranging from six months to two and one-half years, have received combined therapy. Seven of them have required more than one course of treatment, while five responded well to their first course of therapy and at the time of

*Results of Combined Hormone-Mechlorethamine Therapy in Children with Lipoid Nephrosis*

| Case | Course of Combined Therapy | Days of Treatment with Corticotropin (A) or Steroid (S) in the 30 Days Before $HN_2$ Administration | Average Duration of Remissions Before Combined Therapy * | Duration of Remission After Combined Therapy | Remarks |
|---|---|---|---|---|---|
| 1 | I | 28A † | (3) 5 days (5 mo.) | 40 days | Refractory to corticotropin at time mechlorethamine was given |
| | II | 25A † | (0) .. (26 days) | 49 days | Refractory to corticotropin at time mechlorethamine was given |
| | III | 17A | (2) 5 days (40 days) | 45 days | Mechlorethamine was not preceded by 6 continuous days of corticotropin |
| | IV | 20A | (4) 4 days (3 mo.) | 11 mo.+‡ | |
| 2 | I | 8S–13A | (10) 13 days (11 mo.) | 9 mo. | A brief recurrence 14 days after mustard preceded the 9 mo. remission |
| | II § | 16A | (2) 16 days (2 ½ mo.) | 9 days | Failure |
| | III § | 20A | (2) 12 days (1 ½ mo.) | 5 mo.+ | |
| 3 | I | 6A † | (1) 7 mo. (7 mo.) | 17 days | Failure |
| | II § | 21A † | (4) 13 days (7 mo.) | 8 mo.+ | |
| 4 | I § | 21A | (10) 20 days (8 mo.) | 4 mo. | Intermittent therapy, hydrocortisone 30 mg. daily, prior to combined therapy I |
| | II § | 12S–10A | (2) 15 days (1 ½ mo.) | 1 mo.+ | |
| 5 | I | 22A | (2) 5 days (1 mo.) | 3 mo. | |
| | II § | 9S–11A | -- | 1 ½ mo.+ | |
| 6 | I | 6A † | -- | 60 days | Combined therapy given for initial episode † successful |
| | II | 6A † | -- | 7 days | Failure |
| | III | 16A | (2) 6 days (1 ½ mo.) | 37 days | Failure |
| | IV | 21A | (6) 7 days (5 mo.) | 50 days | † successful |
| 7 | I | 15A | (2) 10 days (2 mo.) | 2 mo. | Refractory to corticotropin at time mechlorethamine was given |
| | II | 20A | (3) 12 days (4 mo.) | 2 mo. | Chronic albuminuria (+ to ++) after diuresis without serum biochemical changes |
| | III | 21A | (0) .. (29 days) | 1 mo.+ | Chronic albuminuria persists |
| 8 | I | 17S–6A | (5) 23 days (7 mo.) | 18 mo.+ | |
| 9 | I | 21A | (0) .. (8 mo.) | 9 mo.+ | Albuminuria had been constantly present since onset of disease, 8 mo. before combined therapy |
| 10 | I § | 21A | (4) 8 days (9 mo.) | 5 mo. | Albuminuria recently recurred 5 mo. after combined therapy |
| 11 | I § | 8S–14A | (3) 12 days (2 ½ mo.) | 5 mo.+ | |
| 12 | I § | 21A | (10) 22 days (12 mo.) | 6 mo.+ | Intermittent therapy, hydrocortisone 30 mg. daily, prior to combined therapy |

* Entry in first parenthesis is number of remissions averaged, and entry in second parenthesis is the period of observation before combined therapy. Thus, (3) 5 days (5 mo.) indicates that three remissions of five days' average duration occurred in the previous five months. When more than one course of combined therapy was given, the period of observation is from start of albuminuria after previous course. No entry indicates that assessment of remission duration was not possible.

† Hormones given continuously for indicated number of days prior to injection of mechlorethamine ($HN_2$).

‡ +, disease still in remission at time of writing.

§ Urine free of albumin and disease apparently in remission at the time mechlorethamine was given.

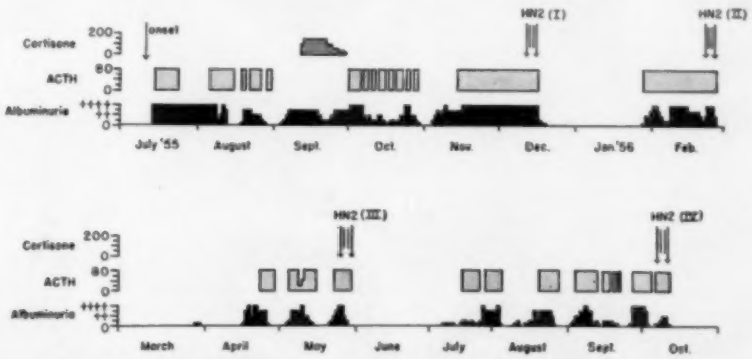


Fig. 1 (Case 1).—Summary of the course and treatment of nephrosis in a 1½-year-old boy. The disease was initially severe and refractory to treatment with corticotropin. The first three courses of combined therapy resulted in relatively long remissions and reduced the severity of subsequent recurrences. The last course resulted in a remission now of 11 months' duration.

writing have not required further treatment. Experience with patients in both these groups is described below. To provide a summary of the data, the course of the disease in each patient before and after combined therapy is given in the Table.

*Patients Receiving Two or More Courses of Combined Therapy.*—Of the seven patients in this group, five could be judged as having, in the over-all view, a good response to treatment. Description of the results in these five patients will be followed by the results in two patients in whom the success of treatment could be judged as only fair.

Case 1 (Fig. 1).—The patient was 1½ years old at onset of disease, in July, 1955. The first corticotropin course, lasting 10 days, had no effect on the edema or albuminuria. With a second 10-day course, started 8 days after completion of the first course, albuminuria cleared, only to recur 5 days later. Thereafter the disease was characterized by almost continual albuminuria despite frequent treatment with corticotropin and cortisone. In the 4-month period from the middle of August to the middle of December, 1955, there were only two remissions, with a total of 11 albumin-free days. During this time, the parents were advised that the child had a poor prognosis for complete recovery. Mechlorethamine was first administered in December, 1955. Administration of the drug was preceded by 28 days of continuous corticotropin therapy, which had failed to affect the albuminuria. With completion of mechlorethamine therapy, a remission occurred lasting 40 days. With recurrence of albuminuria in the latter part of January, 1956, corticotropin was again started and given continuously for 25 days, without remission. Mechlorethamine for a second time was added to the corticotropin regimen, again with a good result. The resultant remission lasted 49 days. The process was repeated (mechlorethamine III) in April, 1956, although on this occasion corticotropin was given during only 17 of the 30 days prior to mechlorethamine therapy and was not used continuously in the 6-day period immediately before mechlorethamine was given. The resultant remission lasted this time for 45 days. During this period the character and severity of the disease appeared to have changed, in that a brief course of corticotropin would clear the albuminuria, albeit for only a short period. In July, August, and September, 1956, corticotropin alone was given for albuminuria to determine whether a spontaneous remission of the duration seen after mechlorethamine administration would occur. When it was apparent that remissions of 2 to 5 days' duration were all that could be expected of this form of treatment, mechlorethamine (IV) was given again in October, preceded by 20 days of corticotropin therapy in the previous 30 days. After this course of therapy albuminuria has not reappeared, the duration of the remission at the time of writing being 11 months. The child has no signs of renal disease.

In summary, this child could be classed as a severe nephrotic in that his condition was initially refractory to hormone therapy and remissions, when they occurred, were of short duration. Four courses of combined therapy were necessary before a long remission was finally achieved. In three of these courses corticotropin was given for 20 or more days in the 30 days preceding mechlorethamine therapy; in one, 17 days of corticotropin therapy preceded mechlorethamine administration. Each time mechlorethamine was added to the corticotropin regimen a diuresis, with cessation of albuminuria, occurred, although on two occasions (mechlorethamine I and II) the disease was at the time unresponsive to corticotropin used alone. All courses of combined therapy were successful in inducing a remission of considerably longer duration than those which followed corticotropin or cortisone therapy alone.

Case 2 (Fig. 2).—The patient was 6$\frac{11}{12}$ years old at onset of nephrosis, in February, 1955. The initial episode was treated successfully with corticotropin. From this date until December, 1955, he had 10 recurrences of the disease, approximately 1 per month, each treated with either corticotropin or steroid. In January, 1956, mechlorethamine was combined with corticotropin treatment. Mechlorethamine administration was preceded by 22 days of therapy with corticotropin and cortisone in the previous 30 days. Albuminuria reappeared two weeks later but disappeared after three days of treatment with steroid. Following this episode there was no evidence of disease, and no treatment was given for a period of nine months. In November and December, 1956, and January, 1957, there were three recurrences of the disease, one coincident with occurrence of chickenpox of not undue severity. In January, 1957, a second course of mechlorethamine was given, which was preceded by 16 days of corticotropin therapy in the previous 30 days. The results were disappointing in that albuminuria returned in nine days. Three exacerbations appeared in the following 45 days. In April,

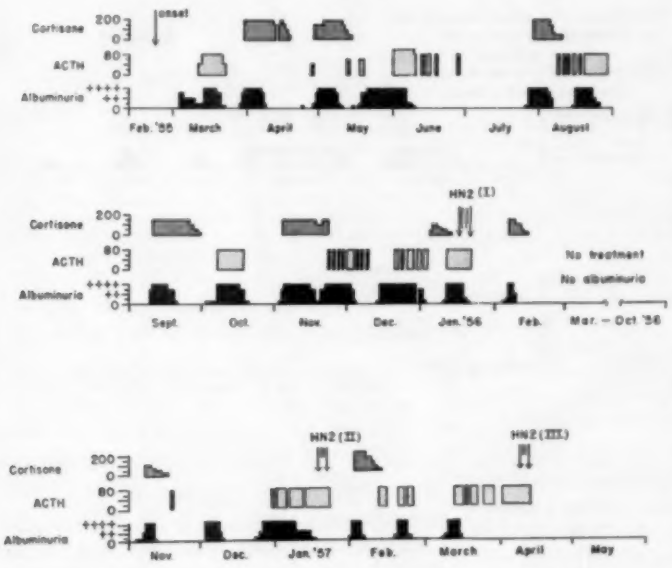


Fig. 2 (Case 2).—Course and treatment of nephrosis in a 6 9/12-year-old boy. After 11 months of disease characterized by frequent recurrences treated with hormone, combined therapy, given in January, 1956, was followed by a remission of 9 months' duration (marred by a brief recurrence in February, 1956). A second course of combined therapy, in January, 1957, did not affect the course of the disease. A third course, in April, 1957, has been followed by a remission now of five months' duration. The two successful courses had 20 or more days of hormone therapy preceding mechlorethamine ($HN_2$) administration, while the unsuccessful course comprised 16 days of hormone pretreatment in the previous 30 days.

1957, another course of combined therapy (mechorethamine III) was given, this time preceded by 20 days of corticotropin therapy in the previous 30 days. At the time mechlorethamine was given the urine had been free of albumin for 24 days. In the five months which have elapsed since this course of therapy, no further episodes of albuminuria have occurred.

The experience with this patient brings up several points. First, it will be noted that two of the three courses of combined therapy resulted in a long remission. In these two (mechlorethamine I and III), administration of mechlorethamine was preceded by 20 or more days of hormone therapy in the previous 30 days. In the course in which mechlorethamine administration was preceded by 16 days of corticotropin therapy (mechlorethamine II), the remission was short. Although there seems little basis for ascribing the differing results to a four-day difference in the duration of the pretreatment period, it will be noted in other patients described below and listed in the Table that a rough correlation between duration of pretreatment and duration of remission exists. Secondly, mechlorethamine I was preceded by administration of both steroid and corticotropin, although the dosage of steroid was small and it was given for only a short time. In this patient, as in others receiving this combination (see below and the Table), a long remission has resulted. In this case, however, the remission was marred by a brief recurrence shortly after cessation of combined therapy. The reason for this short episode is not understood; in no other patient has the disease evidenced similar behavior. Finally, it should be noted that a good result was obtained when the mechlorethamine (III) was administered at a time when the disease was inactive and the urine was free of albumin. The successful result under these conditions has been paralleled by similar successes in other patients (see below and the Table).

Case 3 (Fig. 3).—The patient was 2 10/12 years of age at the time of onset of nephrosis. She initially had mild nephrosis, having only eight episodes of albuminuria in the first 19 months of her disease. The episode of May, 1956, shown at the beginning of the chart, occurred after a seven-month remission. For this episode she was given a course of combined therapy in which only six days of corticotropin therapy preceded administration of mechlorethamine. The result was disappointing in that albuminuria was recorded as

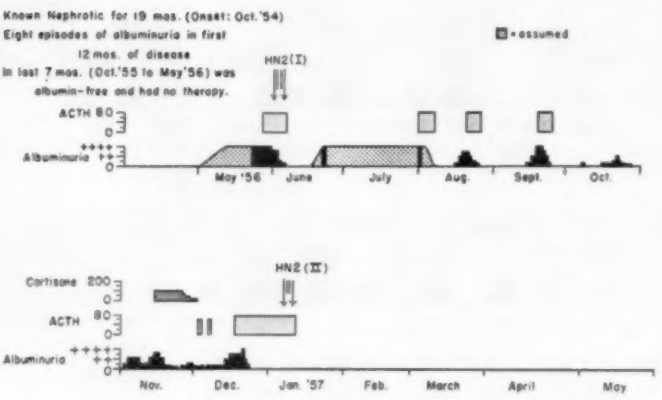


Fig. 3 (Case 3).—Course and treatment of nephrosis in a 4 5/12-year-old girl. The first course of combined therapy, in which mechlorethamine administration was preceded by six days of therapy with corticotropin, was followed by a remission of short duration. The second course of mechlorethamine, in January, 1957, was preceded by 20 days of hormone therapy and has been followed by a remission now of 8 months' duration. In this course mechlorethamine was given while the disease was in remission.

present 17 days after the last mechlorethamine injection and probably was present before this time. The parents during this interval could not be depended on to test the urine regularly. This episode culminated in edema necessitating treatment with corticotropin in August, 1956. During the ensuing five-month interval (August to December, 1956) albuminuria was intermittently present and treatment was with corticotropin or prednisone (Meticorten).‡ In December, 1956, a positive tuberculin reaction was noted for the first time and a history of exposure to active tuberculosis was elicited. For this reason, it seemed wise to curtail the use of corticotropin and cortisone. Accordingly, the child was placed on a prophylactic regimen of isoniazid (Rimifon) and streptomycin, corticotropin was given for 21 days, after which mechlorethamine was added to the corticotropin regimen. In the eight months which have followed this course of treatment there has been no recurrence of albuminuria.

In this patient, mechlorethamine started after 20 days of corticotropin therapy (mechlorethamine II) and, as with Case 2, above, given at a time when the urine was albumin-free resulted in a long remission. The hazard of prolonged hormone therapy in a child recently exposed to tuberculosis and with a positive tuberculin reaction was thus avoided. On the other hand, when mechlorethamine was preceded by only six days of corticotropin therapy (mechlorethamine I) the resulting remission was no longer than would be expected from hormone therapy alone.

Case 4.—The patient was 1 10/12 years of age at onset of nephrosis, in June, 1954. Treatment with corticotropin resulted in a remission. During the following two years there were four recurrences of albuminuria and edema, each necessitating hospitalization and treatment with corticotropin or cortisone. The urine was not regularly tested during this period. In June, 1956, two years after onset, the boy was started on intermittent therapy with hydrocortisone, receiving 30 mg. daily three successive days each week. During the eight months of this regimen albuminuria recurred approximately every three weeks, lasting four to five days. The episodes were treated by increasing the dose of hydrocortisone and giving the drug continuously until the urine cleared. In February, 1957, the boy received a course of combined therapy in which the mechlorethamine was preceded by 21 days of treatment with corticotropin. Urine was negative at the time of mechlorethamine administration. Remission lasted for four months. Return of albuminuria prompted a second course of combined therapy in August, 1957. The boy is still albumin-free, one month following this course.

This boy is one of two in the series in whom intermittent steroid therapy preceded administration of combined therapy. The daily dosage of hormone was, however, small, and relapses occurred frequently. Combined therapy in which administration of mechlorethamine was preceded by treatment with corticotropin for 21 days resulted in a relatively long remission. Again, the

‡ In the Figures, medication with prednisone has been plotted as cortisone, multiplying the prednisone dose by a factor of five. There was no discernible difference between the efficacy of prednisone and that of cortisone.

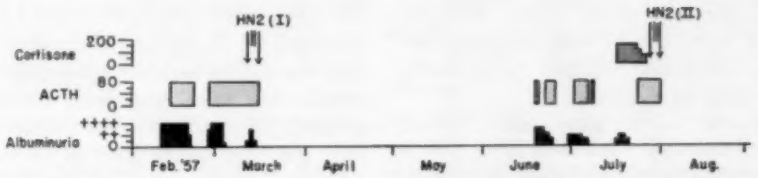


Fig. 4 (Case 5).—Course and treatment of nephrosis in a $5^{10}/_{12}$-year-old boy. Although the disease in this child was sufficiently severe that albuminuria developed while he was receiving continuous corticotropin therapy, administration of combined therapy (March, 1957) was followed by a remission of three months' duration. Recurrence of albuminuria prompted a second course of therapy in July, 1957.

mechlorethamine was given at a time when the urine was albumin-free.

CASE 5 (Fig. 4).—The patient had onset of nephrosis at the age of $5^{10}/_{12}$ years. Corticotropin was initially given for nine days, at which time albuminuria cleared, only to recur one week later. Therapy with corticotropin was again started, and the urine became free of albumin after seven days of treatment. Corticotropin injections were then continued until they had been given for a total of 22 days within 30 days, at which time the hormone therapy was combined with mechlorethamine. Despite the fact that corticotropin was being given continuously in a dosage of 80 mg. daily prior to mechlorethamine therapy, albuminuria appeared just before the first injection of mechlorethamine and lasted three days. Recurrence despite continuous corticotropin therapy suggests that the disease in this boy was severe and potentially refractory to corticotropin. After mechlorethamine treatment the child was albumin-free for three months. With the reappearance of albuminuria, another course of combined therapy was given, with a remission now of 45 days' duration.

Although this boy was not followed long enough prior to therapy with mechlorethamine to assess fully the severity of his disease, the development of albuminuria while he was receiving large doses of corticotropin gives evidence that difficulties were to be expected in the way of refractoriness to corticotropin. A three-month remission followed combined therapy.

The following two patients have responded to combined therapy in a less satisfactory manner than those described above.

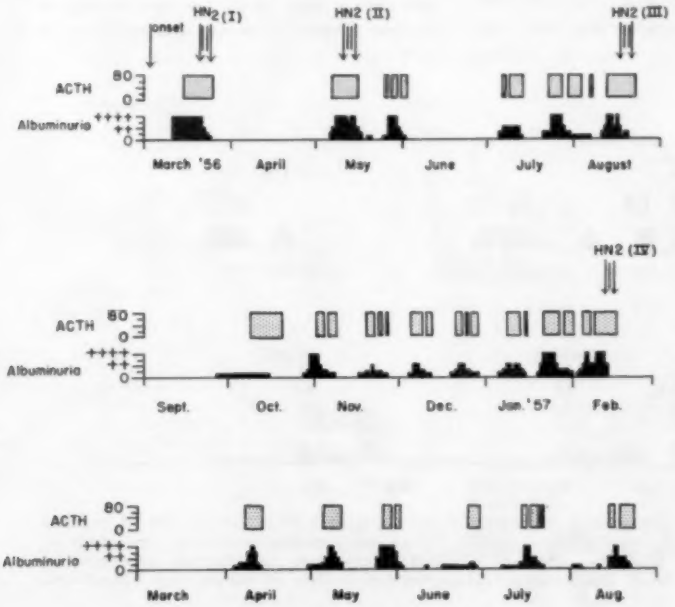


Fig. 5 (Case 6).—Course and treatment of nephrosis in a $1^{3}/_{12}$-year-old boy. Combined therapy in this child has been either questionably successful or unsuccessful in producing a long remission. Of the four courses of therapy given, two (*I* and *II*) have been preceded by only 6 days of hormone therapy; one (*III*), by 16 days, and one (*IV*), by 20 days in the previous 30 days.

In each, the remissions after combined treatment were not of long duration, and one has developed chronic albuminuria, unresponsive to treatment.

CASE 6 (Fig. 5).—The patient, aged 1 3/12 years at onset of nephrosis, was initially given (March, 1956) a course of combined therapy in which six days' treatment with corticotropin preceded the start of mechlorethamine therapy. The consequent remission lasted 40 days. With return of albuminuria a second course (mechlorethamine II) was given, again preceded by six days of corticotropin therapy. On this occasion the remission lasted only one week. Subsequently two further courses of combined therapy have been given. In August, 1956, mechlorethamine administration was preceded by 16 days of corticotropin therapy in the previous 30 days. The urine remained clear for 37 days, and then albuminuria reappeared in trace amounts for 2 weeks. Subsequently, repeated exacerbations led to a fourth course of mechlorethamine, this time preceded by 21 days of corticotropin therapy in the previous 30 days. The resultant remission lasted 50 days. At present, albuminuria is still recurring and being treated with corticotropin. It may be seen, however, that since the fourth course of combined therapy the remissions are somewhat longer than previously and shorter courses of corticotropin therapy are necessary to produce a remission.

As in Case 3, described above, this child (Case 6) had a relatively poor result when mechlorethamine (I and II) was preceded by only six days of corticotropin therapy. Likewise, when mechlorethamine (III) was preceded by 16 days of corticotropin therapy, the results were not spectacular. Evaluation of these responses is, however, difficult, insofar as the last course of therapy, preceded by 21 days of corticotropin administration, resulted in only 50 albumin-free days. The last course of therapy did, on the other hand, appear to reduce the severity of the disease.

CASE 7 (Fig. 6).—The patient was 2 9/12 years of age at onset of nephrosis. Initial treatment was with corticotropin, with prompt remission. A few weeks later a second episode occurred, which cleared without treatment. With a third recurrence, however, the condition became refractory to treatment, and, after 15 days of corticotropin treatment over a 17-day period, mechlorethamine was given. A diuresis promptly occurred, and the subsequent remission lasted approximately two months. When albuminuria recurred, the disease again manifested refractoriness to hormone therapy. On one occasion (February, 1957) 17 days of treatment with corticotropin were required to induce a remission. During this and subsequent episodes the child became very edematous. Although these episodes seemed an indication for further mechlorethamine therapy, family difficulties prevented the boy's hospitalization until May, 1957, at which time a second course of mechlorethamine was given, preceded on this occasion by 20 days of corticotropin therapy in the previous 30 days. Diuresis, with reduction of the

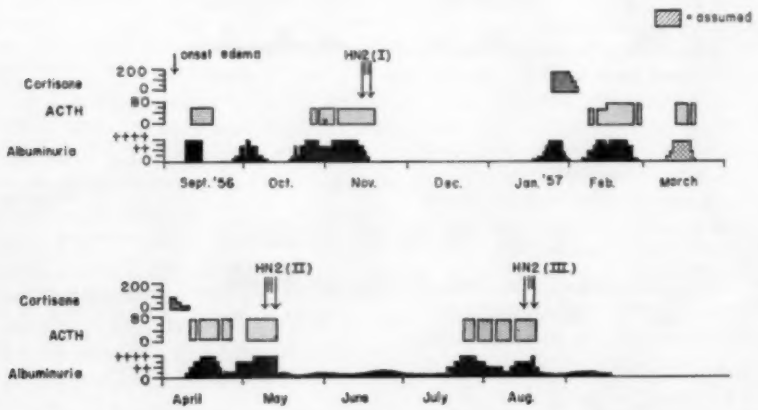


Fig. 6 (Case 7).—Course and treatment of nephrosis in a 2 9/12-year-old boy. Combined therapy administered on two occasions (*I* and *II*) in this boy has resulted in remissions of appreciable duration. However, chronic albuminuria followed the diuresis produced by the second course (*II*). A third course (*III*) resulted in loss of edema, but albuminuria continues.

severity of the albuminuria, resulted, but the urine did not entirely clear; trace to 1+ amounts remained over the next two months. Edema was not present during this time, and the boy felt well. In July, 1957, albuminuria became severer and edema again developed. Again combined therapy with corticotropin and mechlorethamine was used, with diuresis. Albuminuria continues at a low-grade level, but red cell sedimentation rate and serum protein, cholesterol, and urea nitrogen levels are normal.

At the time the first two courses of combined therapy were administered to this patient, the disease was refractory to corticotropin. A remission promptly occurred, however, when mechlorethamine was given. Contrary to the experience with other patients, the severity of the disease was not diminished when it recurred after the first course of combined therapy; refractoriness to hormone therapy was still present. The chronic albuminuria which the child now exhibits is indicative of continuing renal disease, perhaps of a permanent nature. It it possible that this outcome could have been avoided had the second course of combined therapy been given sooner. Despite the chronic nature of the disease, an exacerbation responded to combined therapy (mechlorethamine III).

*Patients Receiving Only One Course of Combined Therapy.*—Five patients are listed in the Table who have responded well to their first course of combined therapy and as yet have not had to have a second course. One of them (Case 10), at the time of writing, has recently developed albuminuria; the other four (Cases 8, 9, 11, and 12) are still albumin-free. One of these patients (Case 11) had had his disease only two and one-half months before administration of combined therapy; the others had nephrosis of long standing.

Patient 9 was a 10-year-old boy who developed albuminuria and edema seven months before combined therapy was given. Although hormone therapy resulted in diuresis, the albuminuria did not clear and was constantly present during the seven-month period before combined therapy was given. The remission following combined therapy has now lasted nine months.

Patient 10 had had onset of disease three years before combined therapy. Although he rarely had marked edema, albuminuria had recurred frequently and had been constantly present in the four-month period before administration of combined therapy. The remission from combined therapy lasted five months before albuminuria reappeared.

Patient 12 had had nephrosis for one year before combined therapy was administered. He had been treated with an intermittent hydrocortisone regimen, as was

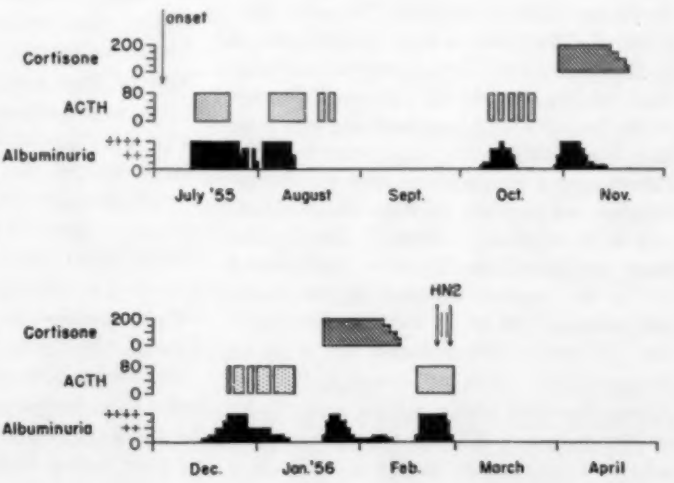


Fig. 7 (Case 8).—Course and treatment of nephrosis in a 2⁹⁄₁₂-year-old boy. After six recurrences of albuminuria in a seven-month period combined therapy was given. Pre-mechlorethamine therapy consisted of 23 days of hormone treatment in a 30-day period, a large part of which was cortisone. The remission has lasted 18 months.

Patient 4, described above, with approximately the same response. Remission has lasted six months following combined therapy.

Patient 8 was one of the first children to receive combined therapy. The course of his disease is described below.

CASE 8 (Fig. 7).—The patient was 2 2/12 years of age at onset of nephrosis, in July, 1955. Initial treatment was with corticotropin for 10 days, following which the albuminuria temporarily ceased but then rather quickly returned. A second course of corticotropin was then given, with a good result. The remission lasted for two months. However, in the five-month period from October, 1955, to February, 1956, there were five recurrences of the disease, each treated with corticotropin or cortisone. In February, 1956, combined therapy was given, mechlorethamine being preceded by 17 days of cortisone administration and 6 days of corticotropin therapy in the previous 30 days. Although at the time mechlorethamine was started edema was developing rapidly, the disease immediately went into remission, with diuresis and cessation of albuminuria. In the ensuing 18 months there has been no recurrence.

This patient has had the longest remission of any in the series. Experience has not been sufficient to relate with certainty the good result to the fact that steroid constituted a large portion of the hormone therapy prior to mechlorethamine administration.

*Relationship of Duration of Hormone Pretreatment to Achievement of a Long Remission After Combined Therapy.*—Because of differences among various patients in the severity of lipoid nephrosis, judgment of the success of combined therapy in producing a long remission is most logically based on previous experience with the patient and a rough assessment of characteristics and severity of his disease. Decision as to whether a course of therapy has been successful has therefore been based not on the absolute duration of the remission achieved but on its duration relative to that of remissions induced by hormone therapy alone. Thus in Patient 1, the first patient described above, with a severe form of the disease, a 50-day remission is considered a satisfactory response, while in a child such as Patient 6, with a relatively mild disease, a 50-day remission would be a questionably successfuly result. These somewhat arbitrary criteria should be borne in mind in assessing the results listed in the Table and summarized below.

Four courses of combined therapy have been given which were preceded by only six days of treatment with corticotropin. Data relative to three of these courses are given in the Table. The fourth course was given to Patient 13, a 6-year-old boy with relatively mild disease which recurred infrequently. The treatment was unsuccessful in that the remission which followed was shorter than usually resulted from hormone therapy alone. In summarizing these results, it can be said of the four short courses given that three have been failures (Cases 13, 3 [I], and 6 [II]) and one has been questionably successful (Case 6 [I]) in inducing a long remission.

Four courses of combined therapy have been given in which mechlorethamine administration was preceded by 15 to 17 days of corticotropin therapy in the previous 30 days. Of these, two (Cases 1 [III] and 7 [I]) could be considered successful and two, unsuccessful (Cases 6 [III] and 2 [II]) in inducing a long remission.

Eighteen courses of therapy are listed in the Table in which mechlorethamine administration was preceded by 20 or more days of hormone therapy in the previous 30 days. Three of these have been given too recently to judge their success (Cases 4 [II], 5 [II], and 7 [III]). Of the 15 remaining which can be judged, 13 can be considered successful and 2, questionably successful in inducing a long remission. Those in whom success is in doubt are Patient 6 (III), who had a relatively mild disease and yet had a remission lasting only 50 days, and Case 7 (II), who had persistent chronic albuminuria following treatment. In the latter case, however, the poor outcome may be the result not of the type of therapy but of poor timing in its administration.

*Relationship Between Type of Pretreatment and Duration of Remission.*—Of the 15 courses of combined therapy with a long pretreatment period in which the results of treatment can be judged, pretreatment was with corticotropin alone in 12 and steroid followed by corticotropin in 3. This distribution is such that no judgment of relative efficacy can be made, but it may be seen in the Table that those courses in which steroid was used have all been successful and some, notably so. One patient had a 9-month remission, and two are still in remission 18 months and 5 months following therapy.

*Use of Combined Hormone and Mechlorethamine Therapy in Patients with the Nephrotic Syndrome with Constant Albuminuria.*—Success of combined therapy in the treatment of pure lipoid nephrosis has led to its use in patients with long-standing disease characterized by chronic proteinuria unaffected by hormone therapy and more-or-less constant alterations in serum constituents characteristic of the nephrotic syndrome (elevation of serum cholesterol and reduction in serum albumin, total protein, and albumin-globulin ratio). All had occasional exacerbations, characterized by increase in the severity of the biochemical changes, increased proteinuria, and edema. Only one had signs of renal insufficiency, with elevation of the serum level of nonprotein nitrogen and a mild acidosis.

In none of these patients were the results of combined therapy impressive, although most seemed to be benefited to some extent and for variable periods. Reduction in the severity of the proteinuria, of the serum chemical abnormalities, and of the edema usually followed treatment, but mild proteinuria persisted. In one patient with very long standing disease there was no biochemical sign of improvement, but the child became more active and felt better. The child with signs of renal insufficiency was not benefited and perhaps was harmed by the treatment.

Experience has been too limited with this type of case to define the place of combined therapy in its management. However, it would appear to be of greater benefit than courses of hormone treatment alone. The contraindication to its use appears to be the same as for hormone therapy, i. e., the presence of permanent renal insufficiency.

*Complications of Combined Therapy.*—No serious systemic reactions have been observed to result from use of the mechlorethamine-corticotropin combination. In the present series of patients no systematic study of the formed elements of the blood to assess the depression of hematopoiesis which follows mechlorethamine therapy has been carried out. None of the patients, however, has shown evidence of or manifested symptoms of bone marrow depression. Several have had acute viral or bacterial infections of the respiratory tract shortly after completion of mechlorethamine therapy, which were of normal duration and severity and without undue complications.

After approximately 10% to 20% of the injections vomiting and/or nausea occurred. With mechlorethamine administration in the evening, as was always the case, the stomach upset was typically present at breakfast time and had disappeared by noon.

A number of the children had local reactions to mechlorethamine therapy consisting of phlebitis at or near the site of injection. The incidence of these has been greatly reduced by (1) injecting into as large a vein as possible, (2) abolishing any tape or other wrapping above the site of injection which might have a tourniquet action, and (3) flushing the vein by allowing the intravenous infusion to flow at a rapid rate for 10 to 15 minutes after the mechlorethamine has been infused.

## Comment

Approximately 80% of the courses of hormone alone given to edematous patients with the nephrotic syndrome are successful in inducing diuresis and remission.[1,3,9] Su-

periority of one type of hormone therapy over the other (corticotropin vs. steroid) has not been demonstrated.[3] Less attention has been paid to use of mechlorethamine as the sole agent in treatment of nephrosis in children, and hence statistics on the incidence of diuresis after its use are less reliable. It would appear to be effective somewhat less frequently than is hormone therapy.[10,11] The present study suggests that combined hormone-mechlorethamine therapy is effective in inducing a remission with greater frequency than is either agent used alone. Combined therapy was administered on 16 occasions to patients with pure lipoid nephrosis at a time when active disease with albuminuria was present. With 14 of these courses albuminuria ceased and diuresis occurred coincident with the administration of mechlorethamine, despite the fact that several patients at the time were refractory to hormone treatment. With two courses, both in the same patient (Patient 7), diuresis occurred but low-grade albuminuria persisted. Similar results have been obtained by Startzman and Mercer.[8] In both of these series, mechlorethamine administration has been preceded by six or more days of hormone therapy. Whether a hormone pretreatment period shorter than six days could be used is somewhat doubtful, judging from the results of a study by Greenman, Weigand, and Danowski.[12] These authors administered 28 courses of corticotropin, each lasting for 28 days, in which mechlorethamine was given in a single dose of 0.3 mg. per kilogram on the third day of hormone treatment. Neither cessation of albuminuria nor diuresis was noted coincident with the mechlorethamine therapy. In fact, in 17 instances low-grade albuminuria was still present after completion of the corticotropin course. Although their treatment regimen differed in many details from that of the present series, the results do suggest that the minimal duration of the priming period with hormone must be six days if remission is to occur in a high percentage of the cases.

Whereas pretreatment for only six days is all that is necessary to produce a remission coincident with mechlorethamine therapy, a much longer period of pretreatment, with development of a definite hyperadrenal state, appears to be necessary if the remission is to be a lasting one. In the present series, mechlorethamine administration after pretreatment with hormone for 20 days or longer resulted, with high frequency, in a remission of greater duration than would have been expected from previous experience with hormone therapy alone. Although the series is small, the close temporal relationship of the long remission to the combined therapy invites the conclusion that this form of management definitely alters the course of the disease. Further evidence of the salutary effect of combined therapy on the disease is the fact that a number of children previously subject to frequent recurrences, especially with infections, have had, after combined therapy, respiratory infections of viral and bacterial origin, often of considerable severity, without developing albuminuria.

The combined-therapy regimen currently in use employs steroid for the majority of the pretreatment period. Use of steroid seems logical for its ease of administration and because the hyperadrenal state is more dependably produced by steroid than by corticotropin. The cases described above in which steroid has been used in the pretreatment period, although few in number, have had good results. In the present regimen, hormone is given for a period of 25 days. On Days 1 to 14 steroid is given. On Day 15 corticotropin injections are started, and on Days 15 to 18 the steroid dose is tapered. Corticotropin is then given daily until Day 25, and on Days 21, 22, 23, and 24 mechlorethamine is administered in a daily dose of 0.1 mg. per kilogram intravenously. The present study has not attempted to determine the optimal doses of hormone in such a regimen. It should be sufficient to produce definite signs of hyperadrenalism—Cushingoid facies, body weight increase of 8%

to 10% in the absence of nephrotic edema, and protuberant abdomen—by the time mechlorethamine is administered. Dosages now in use are, for steroid, 150 to 250 mg. of cortisone or 30 to 50 mg. of prednisone daily and, for repository corticotropin injection, 60 to 100 mg. once daily.

This regimen is not ordinarily instituted with the first episode of disease in the new nephrotic, in view of the fact that a certain number will have no recurrence of the disease after a diuresis produced by hormone therapy alone. When, on the other hand, refractoriness to hormone therapy has become apparent during the first episode, mechlorethamine has been given. Ordinarily the combined therapy described above is reserved for use with the second or third episode of albuminuria, depending on the duration of the hormone-induced remission.

Equally good or perhaps better results might be obtained with a regimen in which steroid is the only hormone used. Since the hyperadrenal state can be produced more quickly with steroid, it is possible that duration of pretreatment could be shortened. One 25-day course such as that described above but in which cortisone was used exclusively has been given without difficulty. It was given too recently to evaluate its effectiveness.

The ability of combined hormone-mechlorethamine therapy to induce a prolonged remission is of interest not only from the therapeutic but also from the theoretic standpoint. Explanation of how combined therapy affects the course of the disease is made difficult by our lack of information about the nature of the disease. In general, however, this lack of information is limited to the details of pathogenesis. Evidence is slowly accumulating which strongly suggests that lipoid nephrosis is basically the result of an immunoallergic response. Briefly, the points in favor of this view are (1) the production in experimental animals of a disease very similar to nephrosis by use of antikidney antibodies; (2) reductions in serum complement level which occur with exacerbations of the disease, with return to normal levels with remission [5]; (3) the recent demonstration by the fluorescein antibody-labeling method that γ-globulin is present in abnormal quantity on the renal glomeruli of patients with nephrosis,[13] and (4) the fact that treatment with corticotropin and cortisone, agents known under certain conditions to inhibit antibody production and to suppress the inflammatory response to antigen-antibody reactions, frequently results in remission of the disease, or, if given while the patient is in remission, prevents further exacerbations of the disease. It thus seems fruitful to consider the action of combined therapy from the standpoint of its effect on immunoallergic phenomena.

As information accumulates concerning the effects of cortical hormones and mechlorethamine on the immune mechanism of the body, it becomes apparent that these two agents in combination might exert a synergistic effect, more striking than the effect of either alone. As an example, Miller, Davison, and Smith [14] have studied the effect of several carcinoclastic agents on the lymphoid system in adrenalectomized and normal animals, using as an index the respiration of the spleen and thymus. Podophyllotoxin, and to a less-certain extent mechlorethamine, was more effective in depressing the respiration of these tissues in the intact than in the adrenalectomized animal. Thus the presence of adrenal glands was in some way necessary for the action of these agents. It is within the realm of possibility that in hyperadrenal states, as in the patients of the present series, certain of the actions of mechlorethamine are markedly different from those in the normal subject.

Further evidence of the possibility of synergism is noted as one compares the effects of hormone and of mechlorethamine on the immune system. Corticotropin and certain adrenal steroids have long been known to have an involuting effect on the lymphoid organs of the body and to pro-

duce lymphocytolysis.[15-17] This involution starts immediately after exposure to these substances and continues for periods of hormone administration up to 20 days in length.[18] The tissues quickly revert to normal when the agents are stopped.[19,20] Production of antibodies to antigens such as egg albumen[21] and Pneumococcus polysaccharide[22] is depressed in experimental animals receiving corticotropin or steroid. It should be noted, however, that this effect varies with the species, the antigen employed, and its dosage.[19] Thus depression of the antibody response to Pneumococcus antigen could not be demonstrated in man receiving corticotropin,[23] nor did cortisone or corticotropin consistently depress the antibody response to large doses of a foreign protein in rabbits.[24,25] In animals receiving two antigens simultaneously, cortisone depressed the antibody response to one but did not affect the response to the other.[26] Thus, in nephrotics receiving corticotropin or steroid it can be assumed that involution of the lymphoid elements of the body occurs, but whether production of the antibodies responsible for the disease is depressed cannot be determined until better methods of identifying and quantitating these antibodies are developed.

Mechlorethamine given by infusion to animals also causes involution of lymphoid tissue and rapid necrosis of the cellular elements thereof.[27-29] The changes in lymphoid tissue in man after therapeutic doses are similar but seem to be less marked than those reported in animals.[30] The involution and degenerative changes are the result of chemical affinity of the mechlorethamine for the proteins of the nuclei of cells, especially those that are rapidly dividing.[27] When it combines with these proteins, cell destruction occurs. There is now considerable evidence that the nucleoproteins most affected are those containing deoxyribose as compared with those containing ribose.[31-33] It is of interest that the suggestion has been made, based on less-well-founded evidence, that deoxyribose nucleoprotein is likewise the cellular substance affected by the adrenal hormones.[34,35] Thus, both these agents affect lymphoid tissue and may perhaps affect a common cell component. The mechanisms of their action, on the other hand, are quite different. The steroid action may be an indirect one requiring cofactors,[35] which results in augmentation of the normal aging process of the cells[34] and prevention of mitosis,[20] while mechlorethamine combines with and directly inactivates the nucleoprotein.

Thus, events in the patient with nephrosis receiving combined therapy may be visualized as follows. By the end of 20 days of hormone therapy a generalized involution of lymphoid tissue and probably a depressed ability to form antibodies to certain antigens is present. Over the next four days this state is maintained by continuing hormone administration, and at the same time mechlorethamine is given, further altering the lymphoid system by a cytotoxic effect. It would seem logical to hypothesize that, through this combined effect, the system responsible for the formation of antikidney antibody is depressed to a greater degree and for a longer time than would be the case after hormone treatment alone; subsequent liberation of antigen from the kidney does not elicit the antibody response necessary for an exacerbation of the disease, and the glomerular lesion responsible for the disease heals. At the cellular level, one can only hypothesize as to the nature of the hormone-mechlorethamine synergism. It could be said that, with the affinity of mechlorethamine for lymphoid tissue, the person pretreated with hormone and with a dearth of lymphoid tissue would have a greater concentration of mechlorethamine per unit of such tissue than would the person not pretreated with hormone. Thus, there would be greater cell destruction and more primitive cell types affected, resulting in a more lasting depression of antibody formation. Evidence against such a hypothesis is the fact that considerable physical reduction in the mass of the lymphoid tissue

occurs after three to six days of hormone administration, and yet mechlorethamine administered after this interval, although in theory similarly concentrated, does not affect the course of the disease. It seems more logical to assume that after 20 days of hormone administration a change, the nature of which is unknown, occurs in lymphoid elements, rendering them more sensitive to the action of mechlorethamine.

Although it seems logical that the action of combined therapy is on the antibody-forming system, there is no real proof for this. Patients subjected to the combined regimen have not had an increased susceptibility or an abnormal response to infection. In unpublished studies it has been found that rabbits treated with a combined regimen similar to that used in patients had only a delay in their antibody response to antigenic stimulation with ovalbumin given three days after therapy ceased. With a second injection of ovalbumin, 10 days later, antibody attained the same level as in normal animals not treated with the hormone-mechlorethamine combination. It is possible that the effect of combined therapy in inhibiting the autoimmune process responsible for the disease may be as much a result of reduction in antigen liberation as an inhibition of antibody formation. It could be visualized that antigen liberation from kidneys not completely healed is responsible for exacerbations of the disease; if such is the case, cessation of albuminuria would not be an index of complete healing. Subjecting the kidneys to the anti-inflammatory effect of hormone for 20 days may be a necessary part of the combined regimen; healing continues after therapy is stopped through a more-or-less-transient depression of antibody formation brought about by mechlorethamine administration. If such were the case, it would seem that a relationship should be observed between the duration of the albumin-free period before mechlorethamine is given and the duration of the remission. Such a relationship seems to be present but cannot be statistically valid within the limited experience of the present study.

## Summary

Combined therapy, consisting of the administration of mechlorethamine (nitrogen mustard) at the end of a course of hormone therapy, has been given on 25 occasions to 12 children with lipoid nephrosis. The disease had been present for more than two and one-half months at the time that 22 of the courses of combined therapy were given. The effectiveness of the treatment has been assessed by comparing the frequency of recurrence of the disease and responsiveness to hormone treatment before combined therapy with the course of the disease after combined therapy.

The results strongly suggest that in children with pure lipoid nephrosis the addition of mechlorethamine at the end of a course of corticotropin (ACTH), or of steroid followed by corticotropin, results in two advantages, providing the period of hormone administration prior to institution of mechlorethamine treatment is of sufficient duration. These advantages are as follows.

1. Remission occurs with high frequency when mechlorethamine is given on the last 4 days of a course of hormone lasting 10 or more days. In all of 16 courses of combined therapy given while the disease was active, diuresis occurred coincident with the administration of mechlorethamine. With all except two courses, albuminuria likewise cleared.

2. The remission will be of greater duration than that observed after hormone therapy alone, providing mechlorethamine administration is preceded by a treatment period with hormone of at least 20 days' duration. Of 15 courses of therapy in which mechlorethamine administration was preceded by 20 or more days of hormone therapy in the previous 30 days, 13 were followed by a remission significantly longer than was observed with hormone therapy alone. The hormone used was either corticotropin or steroid followed by cortico-

tropin. Long remissions resulted whether, at the time of mechlorethamine administration, the disease was active, with albuminuria present, or in remission.

Of four courses of therapy in which mechlorethamine administration was preceded by 15 to 17 days of corticotropin administration in the previous 30 days, two courses were followed by a long remission and two appeared to have little influence on the course of the disease.

Of four courses in which mechlorethamine administration was preceded by only six continuous days of corticotropin therapy, three failed to affect the duration of the subsequent remission and one had a questionably salutary effect.

It is felt that with the modified form of combined therapy now in use (long-term pretreatment with steroid followed by corticotropin) these results may be improved.

### Addendum

In the period following preparation of this report, the patients described have continued to do well. In eight of the patients the disease has remained inactive and the urine albumin-free despite numerous febrile episodes. Thus, for Cases 1, 2, 3, 4, 5, 8, 9, and 12, the duration of the remission after the last course of combined therapy can be increased by six months over the times indicated in the Table. Patient 6, who was considered to have had poor or questionably successful responses to his first four courses of combined therapy, has had a fifth course, with a remission now of five months' duration, the longest observed in this child. Patient 10, whose disease was active at the time of writing, has had a second course of combined therapy, with a remission now of four months' duration. Patient 11 had recurrence of his disease seven months after the first course, and his urine has now been albumin-free for two and one-half months after a second course. Patient 7 continues to have a low-grade albuminuria but otherwise is in good health, with no evidence of renal insufficiency.

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# Pulmonary Edema Occurring During the Course of Renal Azotemia

*Its Differential Radiologic Diagnosis*

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Although azotemia as a manifestation of chronic nephritis and other disease is not uncommon in children, the pulmonary complication seen during the course of azotemia, which we are here describing, seems to be rare. It is the purpose of the present paper to alert the pediatrician to this type of pulmonary edema with the thought that awareness of this picture may not only lead to more frequent diagnosis but may also direct attention to the importance of cardiac compensation in the prevention of pulmonary edema in these patients. In comparison with its frequency in adults, this syndrome is, nevertheless, infrequent, probably because the various components essential to the precipitation of this type of pulmonary edema are not frequently present in children.

Pulmonary edema with azotemia has been repeatedly described in adults [3-5,15-17] but, to the best of our knowledge, has not appeared in the pediatric literature. In adults it is not uncommon, although the paucity of clinical findings makes it easily overlooked.

Gould and Torrance [5] have recently published a roentgenologic analysis of 100 cases of pulmonary edema in adults. By personal communication with Dr. Gould, we learned that azotemic pulmonary edema has been observed in children, although such cases are not included in their report. In their publication they describe pulmonary edema in two categories: acute and chronic. The acute form is not difficult to diagnose clinically, because of the sudden onset of dyspnea, orthopnea, and anxiety. The chronic form, however, is elusive, because of minimal clinical findings and symptoms; in such cases the abnormal chest roentgenogram suggests the diagnosis of pulmonary edema and may also lead to the discovery of coexisting azotemia.

Rendich, Levy, and Cove [15] investigated the radiologic findings in patients with azotemia to determine the existence and frequency of pulmonary edema. Among 50 patients with elevated blood urea, chosen at random, they were unable to demonstrate pulmonary edema radiographically. They concluded that the pulmonary changes in patients with azotemia do not necessarily parallel the elevation of blood urea nitrogen and that the prognosis was related to the rapidity of lung clearing. In this report the status of the heart is not clarified.

Roubier,[16] on the other hand, associates the clearing of the lungs with a fall in blood urea. DePass et al.[22] recently reported their observation of six patients and discussed the controversial terms "uremic pneumonia" and "pulmonary azotemia." They conclude that the roentgenographic appearances represent "pulmonary congestion and edema due to fluid retention from whatever cause, and should not be considered as diagnostic of nitrogen retention caused by renal failure." These are only a few of the investigators who represent different points of view concerning the cause of so-called "uremic pneumonia."

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Pathologic studies of pulmonary edema began with Welch,[1] in 1878, when he demonstrated experimentally its cardiac mechanism. In 1932 the lung changes in three patients dying of Bright's disease were reported by Ehrich and McIntosh.[2] Bass, Greenberg, Singer and Miller[4] reported that the pulmonary pathologic changes in uremia consisted in hyaline membranes and hyaline deposits in the alveoli, particularly in those patients with glomerulonephritis; the extent of the pathology is proportional to the chronicity. These findings are not, of course, specific for the uremic lung.[6-14] Consolidation of the lung, as sometimes seen in autopsy, has led to the use of such terms as "uremic pneumonia" and so-called "rheumatic pneumonia."[6-14]

The histologic study of this "solid" edema in uremic edema made by Doniach[17] revealed the presence of a fibrinous or an albuminous intra-alveolar exudate with a mononuclear-cell reaction. Hyaline membrane lining the alveolar ducts was also noted. In the experience of Doniach, there is more likelihood of survival in a condition of purely albuminous edema than there would be in a condition of superimposed fibrinous pulmonary edema.

The diagram here reproduced (Fig. 1) illustrates various physiologic mechanisms for the production of pulmonary edema. A common factor in the pathogenesis of the lung lesions appears to be recently altered capillary permeability, the exact nature of which is not fully understood. It is well known that patients with persistent azotemia due to nephritis almost invariably have hypertension and varying degrees of left ventricular strain and enlargement, as well as the increased capillary permeability associated with hemorrhagic tendency. The background for pulmonary edema is therefore manifest. The extent to which this edema is influenced by the azotemia is unknown, but its presence does not necessarily coincide with the clinical manifestations of cardiac failure.[21]

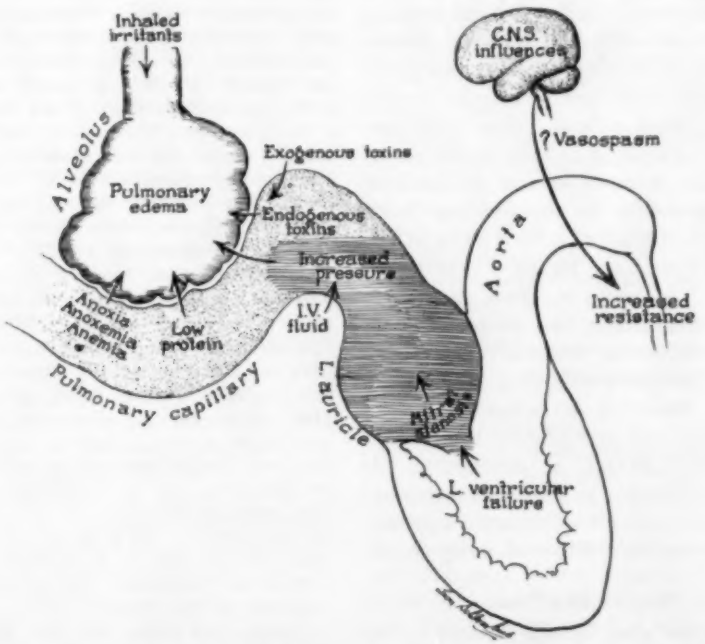


Fig. 1.—Diagram of factors in formation of pulmonary edema. (Reproduced with permission from Gould and Torrance,[5] *American Journal of Roentgenology.*)

### Radiologic Features

The pulmonary patterns of venous dilation and engorgement are representative of the process leading to pulmonary edema. According to Gould and Torrance,[5] enlarged and dilated pulmonary vessels, such as are seen in mitral stenosis, in Eisenmenger's complex, and in other septal defects, present sharp outlines. The dilated pulmonary vessels of chronic passive congestion resulting from hypertension present hazy outlines, presumably due to interstitial edema and very small collections of alveolar fluid. Obliteration of vascular markings with definite clouding of the lung is noted in pulmonary edema from the accumulated alveolar fluid. The air-containing bronchi which traverse the fluid-filled alveoli are relatively radiolucent, and this provides an additional feature of diagnostic importance: "visible bronchial tree" of Fleischner. A well-defined and dense type of central edema without associated congestion is seen in both primary and secondary renal disease, according to Gould and Torrance, and as a consequence there may be minimal findings on physical examination. A poorly defined central edema of lower density associated with congestive changes is seen in cardiac pulmonary edema without uremia. This central pulmonary edema is seen on the roentgenogram as a dense central or perihilar opacity, spreading to the midlung fields bilaterally and leaving a clear zone at the apices, periphery, and the lowest portion of the bases. In addition, there is usually cardiac enlargement. The peripheral clear zone may be due to "relatively greater excursion of the peripheral lung, which gives rise to a squeezing or bellows-like effect most pronounced immediately beneath the chest wall."[5] Dock,[20] in designating this radiologic feature as "hilar hyperemia," states that it is the acidosis and air hunger which prevent the collapse of many alveoli.

### Report of a Case

A 10-year-old white boy was admitted to University Hospital for the 12th time on Oct. 12, 1954. The chief complaints were leg and back pain, fever, and diarrhea for two weeks. A diagnosis of nephrosis had been made when this patient was 2½ years old. He had been severely ill with markedly impaired renal function since that time. Severe hypocalcemia with extensive central nervous symptoms left this boy crippled at the age of 3 years. He presented the picture of a postencephalitic quadriparalytic child.

He had had frequent hospital admissions for edema and infections requiring antibiotic therapy, and on two occasions, digitalization. On each admission there was severe acidosis, hyperproteinemia, and hypercholesteremia. The blood urea nitrogen was variable, often high (up to 36 mg/100 cu. mm.). The low serum calcium responded to calcium gluconate therapy.

*Present Illness.*—For two months prior to the terminal admission the patient had diarrhea, which appeared during the period of increased calcium medication. For two weeks he had intermittent fever, low back pain, and pain in the legs. A diagnosis of enteritis was made. For some time the patient had shown very low blood serum calcium (from 5.2 to 5.6 mg.) associated with a low serum protein of 5.2 to 5.5 mg., without clinical manifestations or tetany.

*Physical Examination on Admission.*—Examination revealed an undernourished, underdeveloped boy who appeared much smaller than his stated age of 10 years. He was in no distress. His general appearance was that of a child with cerebral palsy, with slow unsteady gait and slow movements generally. The lungs were clear; the heart rate was 120; a soft apical systolic murmur was heard. The abdomen was soft; the liver edge was 2 cm. below the costal margin. The extremities appeared wasted and were moderately hypertonic. The blood pressure was 162/112; there was no edema. The admitting diagnosis was that of a nephrotic syndrome, postencephalitic quadriparesis, and hypocalcemia without tetany.

On this admission the blood chemistry studies were not unlike those seen previously, as stated above. The red cell count was 2,500,000 per cubic millimeter, and the hemoglobin was 6.8 gm. The white cell count was normal. Examination of the urine revealed a fixed specific gravity, around 1.040, uncorrected for albuminuria, and various microscopic elements, showing at times white blood cells, hyaline casts, and, on several occasions, red blood cells. An electrocardiogram three days after admission showed the auricular and ventricular rate to be 110 and of a regular rhythm, with prolonged Q-T interval; the prolongation appeared to be in the ST segment. The tracing was strongly suggestive of hypocalcemia.

*Course.*—The patient did well until the 17th hospital day, when he awoke complaining of abdominal pain, appeared uncomfortable, and refused

Figure 2

Fig. 2.—Central pulmonary edema in the child here reported. Note the cardiac enlargement (left ventricular) and symmetrical hilar engorgement extending into the midlung fields, with clear peripheral zones. A small amount of pleural fluid is present at the left costophrenic sinus.

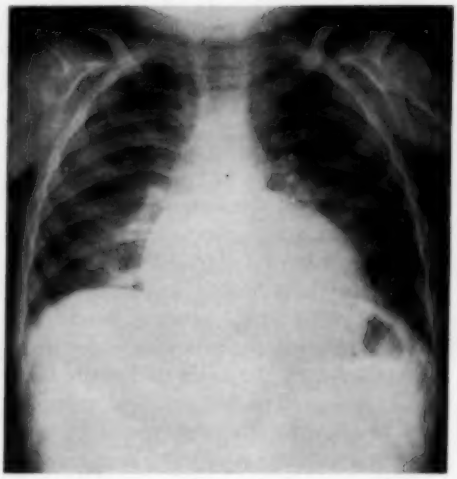

Figure 3

Fig. 3.—Same patient as in Figure 2, forty-eight hours later, after digitalization. The edema has cleared considerably.

breakfast. He had been sitting up in bed the night before, watching television, and had appeared comfortable; just before retiring he complained of a headache. At noon of the 17th hospital day the patient was drowsy, febrile (temperature of 101 F), and nauseated. His headache became severe, and he vomited once. The following day he suddenly became dyspneic and cyanotic and complained of a pain in the chest. He improved after a few hours in an oxygen tent; however, respirations remained about 40 per minute, and auscultation revealed numerous coarse rales. The liver had become further enlarged, being palpable 4 cm. below the costal margin; the right upper quadrant was tender. There was no cough, and there was no evidence of upper respiratory tract infection. A gallop rhythm was heard in the heart for the first time.

An x-ray taken of the chest on the 18th day is shown in Figure 2. On cursory inspection the lung lesions suggested miliary tuberculosis, but there were no enlarged mediastinal or peribronchial nodes (Fig. 4). The roentgenogram, which showed left ventricular cardiac enlargement; large, dilated pulmonary vessels with hazy outlines, and central clouding with clear peripheral lung fields, suggested the probability of pulmonary edema on an azotemic basis. The elevated blood urea (57 mg.), the negative tuberculin test, and the blood pressure of 162/112 confirmed the diagnosis of congestive heart failure in a patient with pulmonary edema associated with azotemia.

Digitalization was begun; antibiotics were given, and repeat blood chemistry studies were made. Within 48 hours of digitalization the patient was improved, the respirations were slower, and the temperature had returned to normal. There was marked improvement in the extent of the pulmonary edema, as seen in the roentgenogram (Fig. 3). The blood urea nitrogen, however, was unchanged (57 mg.).

Although the patient recovered from this acute respiratory distress, he became progressively worse after a short while and developed symptoms such as numerous tarry stools and coffee-ground vomitus; the blood urea nitrogen elevation was 175 mg/100 cu. mm. He died on the 37th hospital day, approximately 15 days after the lung roentgenogram shown in Figures 2 and 3. He showed no pulmonary changes clinically and no dyspnea during those 15 days, although the blood urea rose. Unfortunately, a terminal roentgenogram was not obtained.

*Necropsy.*—The kidneys were small and granular, and the microscopic changes were typical of chronic glomerulonephritis. A small amount of fibrinous exudate was present in the lungs, and the liver cells contained small vacuoles of fat. The left cardiac ventricle was hypertrophied and dilated; the aorta showed "scattered, small yellow atheromatous foci throughout; there are also vascular lesions, mainly arteriolar sclerosis such as are found in hypertension." There was minimal focal fibrosis of the leptomeninges. Elsewhere the

changes were those of passive congestion of the viscera.

## Comment

*Interpretation of Case Presentation.*—The cause of the transient pulmonary edema in this patient remains to be interpreted. The rapid clearing of the lungs after digitalization is strongly suggestive of recovery from hypertensive heart failure. The central distribution of lung lesions is compatible with pulmonary edema; the enlarged heart is like that often seen in patients with hypertensive heart disease on the basis of impaired kidney function. The patient here presented died two weeks after an episode of acute respiratory embarrassment. There are three elements, therefore, involved in this episode, namely, heart failure, kidney disease, and pulmonary infection. Subsequently, he failed to show another episode of pulmonary edema clinically, in spite of rising blood urea nitrogen, but the patient was digitalized throughout this time and showed no evidence of heart failure. The microscopic sections of the lung revealed only minimal changes, which is compatible with clearing from an apparently acute pulmonary edema with left ventricular failure. This could account for a relief of congestion in the pulmonary circuit.

Doniach [18] suggests that there are factors other than that of the intensity of heart failure which may modify the pulmonary picture: uremia, severe anemia, and superimposed respiratory tract infection. In our case, the first two factors were clearly involved. The third factor, that of infection, may have been present at the time of the acute pulmonary edema and may have subsided during the few weeks before death; a mild chronic pulmonary inflammation in the microscopic examination of the lungs is consistent with this theory. The possibility of a low-grade viral respiratory infection, rather than bacterial, is suggested, because of the clinical picture and the ineffectual antimicrobial therapy. The minimal pulmonary findings at necropsy could very well be explained as a residual of a mild chronic, even subclinical, viral infection occurring some two or three weeks before death.

*Differential Diagnosis.*—There is often a discrepancy between a chest roentgenogram, revealing evidence of diffuse disease, and the clinical signs and symptoms of a disease process. The x-ray may be the first directive toward the discovery of such pathology as pulmonary edema, sarcoid, chronic miliary tuberculosis, and, in some instances, cystic fibrosis of the pancreas. True parenchymal inflammatory lesions or even neoplastic infiltrations may simulate pulmonary edema. Laboratory and other tests such as tuberculin reaction and biopsies, as well as the clinical picture, are necessary for final diagnosis.

Pulmonary edema is readily distinguishable from consolidation due to bacterial or infectious pneumonia. The "visible bronchial tree" discussed by Fleischner [19] merits further emphasis and is particularly important in pediatrics. Air-filled bronchi are not visible on the roentgenogram of the normal lung. Visibility of air-filled bronchi may be an indication of fluid-filled alveoli or of peribronchial consolidation, even when present to a small degree.

The distribution of the lesions may be important in etiologic consideration. The "bat's wing" appearance described in edema associated with azotemia is fairly characteristic. Localized or focal pulmonary edema with a lobular distribution or a diffuse type with patchy densities may prove confusing, and these conditions probably cannot be differentiated conclusively on the roentgenogram alone. In cystic fibrosis of the pancreas, lung infections frequently occur and are associated with many different secondary etiologic agents; hence, the x-ray picture is protean in nature. In this disease the symmetrical distribution, especially in the perihilar areas, may closely resemble that of central pulmonary edema. This marked similarity is seen by comparing Figure 4 with that of the patient here reported (Fig. 2). One of the greatest roentgen aids in the differential diagnosis is the size of the

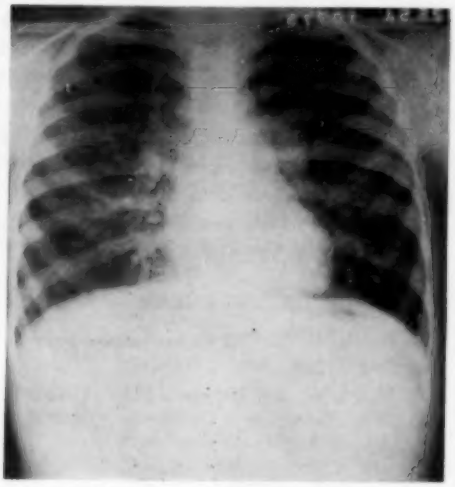

Fig. 4.—Bilateral bronchopneumonic changes associated with infantile cystic pancreatic fibrosis. The differentiating features from those of Figure 2 are the enlarged peribronchial nodes, emphysema, peribronchial infiltration, and microcardia.

heart. Microcardia is invariably present (probably due to emphysema), up to the terminal onset of cor pulmonale, in these patients with chronic pulmonary disease.

Pulmonary edema may simulate diffuse miliary tuberculosis (Figs. 2 and 5). In tuberculosis, as can be seen in Figure 5, mediastinal and bronchopulmonary nodes are frequently enlarged, and sometimes there is calcification. Acute miliary tuberculosis presents foci of even distribution throughout both lungs, extending to the periphery and involving apices and bases alike. However, cardiac enlargement is not a feature of tuberculosis, and there is no evidence of congestion. In acute pulmonary edema rapid clearing of the lungs after appropriate threapy leaves no doubt as to the diagnosis.

Roentgenograms of patients with Loeffler's syndrome, and occasionally those with atypical pneumonia, may also clear rapidly, but not as quickly as is seen in the case of pulmonary edema; the presence of eosinophilia together with the clinical picture is valuable in making a diagnosis. An aid in the differentiation of Boeck's sarcoid and some other acute respiratory diseases is the presence of enlarged mediastinal lymph nodes, a feature not found in pulmonary edema.

*Pathological Physiology.*—In considering the various points of view concerning the picture of pulmonary edema associated with azotemia described in this paper, certain observations may be made. It has not been a common pediatric observation. It would appear that heart failure and azotemia are coexisting features. We should like to suggest that a third factor, that of extensive vascular pathology, not only increased capillary permeability but also atherosclerosis, may play a vital role in the precipitation of pulmonary edema. In the patient here described, there was pathologic evidence of

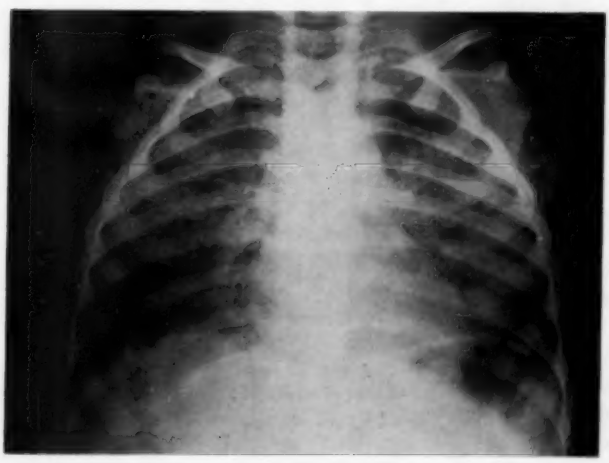

Fig. 5.—Bilateral symmetric distribution of multiple small lesions in acute miliary tuberculosis, with extension of the infiltrations to the periphery. There is a slight degree of lymphadenopathy, with widening of the mediastinum. The heart is normal in both size and shape.

atherosclerosis of the aorta. If the present theory is valid, it would account for the rarity of pulmonary edema in children with azotemia.

We would further explain this rarity by emphasizing that pulmonary edema with renal azotemia may be transient; although its actual occurrence is undoubtedly rare, it might, perhaps, be diagnosed more frequently if we were to look for it. We believe, however, that its infrequency in children as compared with its incidence in adults is due to the fact that vascular pathology such as atherosclerosis is not frequently present in children. In support of the critics of the terms "pulmonary azotemia" and "uremic pneumonia," who deny that uremia alone is responsible for the pulmonary pathology, is the fact that this patient did not develop a second bout of pulmonary edema even though the blood nonprotein nitrogen continued to rise. During this time, however, the cardiac status in this child was improved and evidence of clinical failure did not appear. Thus, this latter feature of the proposed triad in the mechanism of the syndrome, namely, heart failure, azotemia, and extensive vascular damage, was not present.

## Summary and Conclusions

An instance of pulmonary edema occurring in a child with chronic glomerulonephritis is cited. The importance of cardiac compensation is indicated. The chest roentgenogram may be helpful in evaluating the cardiopulmonary status in the detection of pulmonary edema during azotemia. Immediate improvement may be observed in some patients whose heart failure is controlled through digitalization and appropriate therapy.

The similarity of the radiologic findings in azotemic pulmonary edema to that of miliary tuberculosis and other types of diffuse pulmonary lesions is shown in this paper. Pulmonary edema with renal azotemia, although rarer in children than in adults, may be diagnosed more often by use of the roentgenogram of the chest, since the episode may be acute, transient, and sometimes asymptomatic. It is suggested that arteritis may play a role in the production of pulmonary edema occurring during the course of uremia, and that the term "uremic pneumonia" is a misnomer.

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# Skull Dehiscence and Dural Laceration in Unrecognized Familial Craniostenosis

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The remarkably rapid rate of growth of the infant brain challenges all physicians to protect it in the first year of life. Dural laceration associated with a separation skull fracture is not an unusual occurrence in childhood. However, when this injury is associated with unrecognized craniostenosis the course of the disease and its management present interesting problems and emphasize the importance of aggressive treatment planned to allow maximum brain expansion.

Craniostenosis is an unusual anomaly in which the cranial sutures close prematurely, restricting growth of the intracranial contents and causing distortion of the normal development of the skull. Skull expansion is limited by premature suture fusion and progresses most rapidly in the direction allowed by the suture lines which remain open. Scaphocephaly, the commonest variation, is produced by early closure of the sagittal suture and leads to anteroposterior lengthening of the cranium. Brachycephaly (acrocephaly), with increased transverse diameter of the head, is due to early fusion of the coronal or the coronal and lambdoid sutures. Oxycephaly results from early closure of all of the cranial sutures and causes a small skull with peaked vertex. Asymmetrical closure leads to an irregularly shaped head which is denoted as plagiocephaly.

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The etiology of this disease is unknown but is probably an inherent defect in mesenchymal germ plasm. This theory is supported by the frequent association of this disease with other congenital anomalies, by its greater incidence in males than in females, and by its occurrence in siblings and successive generations.[1]

In addition to the apparent cranial deformity, the significant signs and symptoms of craniostenosis may include increased intracranial pressure with its associated physiological changes, abnormalities of the eyes, mental retardation, convulsions, and other congenital lesions.

The cranial deformity becomes apparent sometime in the first year of life. Often it is confused with molding of the head during labor. Experience shows, however, that early synostosis leads ultimately to severer deformity; thus, when the abnormal shape does not disappear during the early weeks of the postnatal period x-ray examination is indicated to rule out craniostenosis.

Eye abnormalities are frequent and in general are a result of change in configuration of the orbit or of early closure of the facial sutures. Exophthalmos, widely separated bulbs, and strabismus are not uncommon. Papilledema, optic atrophy, and blindness develop, due to anatomical distortion of the optic foramina or prolonged increased intracranial pressure.

The degree of mental retardation is roughly proportionate to the restriction of normal cerebral growth, though it is occasionally due to associated brain anomaly. Early surgical treatment may arrest the progress of mental deterioration and im-

prove learning ability.[5] Convulsions are usually a late complication due to the changes brought about by brain injury.

The congenital anomalies which have been noted to occur with statistically significant frequency in patients with craniostenosis include agenesis of the corpus callosum, hypertelorism, porencephaly, syndactylism, choanal atresia, cleft lip and palate, spina bifida, congenital heart disease, and genital abnormalities.

Roentgenographic findings are conclusive in establishing the diagnosis.[2] These include obliteration of the involved suture lines, increased density of the cranial bones adjacent to the fused suture, and the characteristic shape of the skull. Convolutional atrophy of the skull, shallow orbits with vertical orbital plates, small paranasal sinuses and foramina, and platybasia may be seen. Microcephaly, due to failure of growth pressure from the underlying brain can be differentiated from that due to premature closure by the persistence of clean-cut suture lines even though the fontanel may close early.

The aim of treatment in craniostenosis is directed toward decompression of the cranial cavity by release of growth restraint. This permits cerebral growth and development to assume a normal chronological rate. Best results are obtained in the very young age group. The treatment of choice is removal of the fused suture lines by linear craniectomy (synostectomy). The free bone edges may be covered with some growth-restricting substance such as tantalum or plastic film to prevent rapid reclosure of the sutures. Methods of dividing the skull into free-floating fragments (morcellation) and subtemporal decompression have had some success, particularly in older children. However, surgery may be recommended and is well tolerated any time after the second week of life.

The success of treatment depends upon accurate diagnosis, early intervention, and the condition of intracranial structures at the time of surgery. Mortality and morbidity are low in all reported series.[3,4] Postoperative complications are ordinarily not debilitating, though persistent fluid accumulation due to foreign bodies and exposed medullary bone surface may extend the period of hospitalization. These accumulations rarely become infected if carefully handled. The incidence of reoperation necessitated by bone closing the defect produced by synostectomy is decreased by covering the bone edges. Nevertheless, about 20% of the patients require some additional "slotting," owing to the strong tendency for the sutures to reclose rapidly even over the covered bone edges.

The following case history presents an interesting example of familial craniosynostosis in a child whose mother had this condition. It illustrates the changes that occur with associated separation skull fracture and emphasizes the potential brain growth pressure. A method of management for this combination of fracture and premature suture closure is outlined.

## Report of a Case

A 3-month-old white girl was admitted to the neurosurgical service of Children's Hospital, Columbus, Ohio, on Oct. 18, 1956. She was well until 9:30 a. m. on the day of admission, at which time she fell from a 3 ft. table to a concrete floor, striking her head on the right parietal region. She did not appear to lose consciousness and cried immediately, but a swelling rapidly developed on the right side of her head. She was admitted to the hospital through the emergency room one hour after injury.

Birth and development were apparently normal. The child's only sibling, a 20-month-old sister, is well, with no obvious abnormalities. Significantly, her mother had had several operations (starting at the age of 8 months) for premature closure of the sagittal suture, with satisfactory decompression, but impaired hearing and vision remained unimproved. There was no other craniostenosis in the family history.

The child weighed 11 lb. 8 oz. and was well developed and well nourished. She appeared intermittently irritable and drowsy but responded to painful stimuli by crying vigorously. Her temperature was 99 F; pulse rate, 132; respiration rate, 40. There was slight exophthalmos, with a long and narrow head, measuring 16 in. in circumference. There was a 3×3×2 cm. fluctuant right

Fig. 1.—Posteroanterior skull x-ray shows right parietal linear skull fracture with separation of fragments (Arrow *a*), increased bone density adjacent to prematurely fused sagittal suture (Arrow *b*), narrow head, and convolutional atrophy of the skull.

parietal soft tissue swelling. Neurologically she presented bilateral ankle clonus with Babinski responses, moderately increased deep tendon reflexes, absent abdominal reflexes, and apparently normal sensory perceptions. Bilateral syndactylism of the second and third toes was noted incidentally.

Skull x-rays demonstrated a soft tissue swelling in the right posterior quadrant, with a 0.5 cm. wide radiolucent fracture line in the underlying parietal bone. The sagittal suture was obliterated, and this, in combination with the long narrow head and convolutional atrophy, suggested associated craniostenosis of the scaphocephalic type (Fig. 1).

The patient's ankle clonus and Babinski responses subsided shortly after admission. She became alert and active. Body temperature increased to 101 F rectally the day after admission, though there was no evidence of infection. The fever gradually subsided. There was no further change in her neurological status during the first six days. Coronal subdural taps were negative.

After seven days of observation she was taken to surgery for debridement and sagittal craniosynostectomy. The skin incision allowed escape of macerated brain fragments from the subgaleal fluid collection, which overlay a 5 cm. dural laceration under the transverse fracture line. The laceration terminated just short of the sagittal sinus. A 2 cm. midline strip of bone was removed from anterior to posterior fontanel over the sinus and enlarged at the site of dural laceration to allow access to the dural margins. After debridement the margins of the tear were closed with a free graft of cranial periosteum. The sagittal bone margins were covered with polyethylene film secured in place by 0000 black nonabsorbable surgical (silk) sutures. Recovery was uneventful, and the patient was discharged from the hospital on the seventh postoperative day.

*Second Admission.*—Three months later and approximately one week prior to readmission the patient's mother first noted recurrence of a bulge at the operative site. The child was 6 months old and had otherwise progressed well.

She was alert, active, and cheerful; appeared well, and weighed 17 lb. 8 oz. The mass was 10 cm. in diameter at its base, elevated approximately 4 cm. above the level of the scalp, and overlay the area of previous dural repair. Neurological examination showed minimal left hemiparesis. Skull

Fig. 2.—Parietal bone margins have separated an additional 6 cm. since removal of 2 cm. of sagittal suture and adjacent bone three months previously.

films showed that the synostectomy groove had spread from 2 to 8 cm. in width under the pressure of growth of the child's brain (Fig. 2). It was concluded that a hernia had developed at the site of the previous dural repair.

On Jan. 9, 1957, the previous scalp incision was excised, and a 3 cm. rupture was found at the site of the periosteal graft. In addition to fluid in the subgaleal space, several grams of ischemic cerebrum protruded through the defect and had to be excised. Apparently the periosteum was not strong enough to withstand the sudden spurt of brain growth and some brain had extruded as though evacuated under pressure. A flap of dura was mobilized and rotated to close the opening, which was small and immediately adjacent to the sagittal sinus. To strengthen the entire area two additional layers of pericranium were sutured over the defect. The parietal bones with their polyethylene wrapping were widely separated, and there was no evidence of new bone formation. The dura between the free edges had become thick and fibrotic and presented an almost cartilagenous resistance to external pressure. It did not bulge above the contour of the cranium. Some consideration was given to placing a bone graft over the fracture defect, but it was elected not to add additional foreign body to the existing situation.

A subgaleal fluid accumulation developed postoperatively but gradually subsided with repeated aspirations in the ensuing three weeks. The patient did not develop any additional neurological deficit and has shown approximately normal growth and development and no recurrence of the hernia up until the time of her last evaluation, at 11 months of age. The minimal left hemiparesis is no longer grossly detectable.

## Comment

The child, who was 3 months old at the time of her accident, had apparently been asymptomatic until she suffered a head injury. At that time x-ray examination of the skull demonstrated not only the presence of a separation skull fracture but also premature closure of the sagittal suture with accompanying skull deformity. Although craniostenosis could have been more strongly suspected by the history of a similar disorder in her mother, the characteristic x-ray findings were necessary to confirm the diagnosis. This sequence of events emphasizes the need for early x-ray examination if a child's head remains oddly molded or does not grow at the expected rate.

The significant x-ray findings observed in this case include complete obliteration of the sagittal suture line, dense calcification of the bone adjacent to the area of synostosis, early scaphocephalic configuration, convolutional atrophy, and fracture in the thin bone adjacent to the prematurely closed suture. A soft tissue mass visible on the films over the fracture line was caused by extravasation of cerebrospinal fluid and brain under the galea. This fluctuant swelling is frequently seen over dural laceration due to skull fracture in childhood.

The optimum time for surgical intervention was carefully considered prior to exploration in this case. Seven days were permitted to elapse after the injury before craniotomy was done. In this interval subdural and intracerebral bleeding had resolved or were clearing, the period of general and local cerebral edema had largely passed, and demarcation of devitalized brain tissue was well established. It is felt that this delay may well be indicated in similar situations where the child's clinical condition will allow it and that it may save a significant amount of soft edematous brain tissue which might be lost with immediate debridement of the area.

The procedure performed consisted of a linear craniectomy with excision of the sagittal suture and its dense calcifications from anterior to posterior fontanels. The results and the effects of time and growth could easily be seen when repeat x-rays of the skull were taken three months later. At that time there was expansion of the cranial vault, with wide separation of the parietal bones. This separation was certainly caused by the expansion of the growing brain, which was no longer restricted by premature sagittal fusion. This finding points out that the increase in skull size is largely dependent upon the pressure of brain growth and may be limited by inflexible early closure of cranial sutures.

During the first year of life the brain normally almost triples in weight while the

skull is gaining more than 50% of its lifetime increase in circumference. Limitation of growth and expansion by craniostenosis is further emphasized in the above case by rupture which occurred at the point of least resistance as the brain rapidly expanded following excision of the restraining suture. The cerebral growth pressure was apparently of such magnitude that it was capable of stretching and finally tearing the periosteal graft, although the dura had sufficient resilience to stretch more slowly and evenly.

## Summary

The case of a 3-month-old girl with unrecognized familial craniostenosis and an acute traumatic widely separated linear skull fracture and dural laceration is presented.

Further evidence is presented to substantiate the thesis that skull expansion is largely secondary to pressure from normal brain growth.

Arrested or retarded skull growth and unusual head shape indicate the need for early x-rays to confirm the clinician's suspicion of craniostenosis.

If possible, operative intervention for a separation skull fracture with dural laceration and brain herniation should be postponed to seven days, until bleeding has resolved, cerebral edema has subsided, and devitalized brain tissue has become demarcated to facilitate more accurate and conservative debridement.

It is shown that the rapid brain expansion following synostectomy for craniostenosis jeopardizes any site for dural repair.

The evidence of associated congenital anomalies and occasional hereditary cases, as well as the lack of evidence for other etiological factors, favors the thesis that craniostenosis is determined by an error in germ plasm.

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# Adenoids and Hearing Loss in Children

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Opinions differ widely as to the indications for adenoidectomy in children. These differences range from the routine performance of adenoidectomies on almost all children having recurrent upper respiratory infections to the opposite extreme of never removing the adenoids unless there is complete obstruction of the nasopharynx.

Eley [1] stated that an adenoidectomy is indicated when the lymphoid tissue ". . . offers a hazard to the general health of the patient." Johnston and Watkins,[2] on the basis of 600 questionnaires to parents whose children had had tonsillectomies and adenoidectomies, concluded that seven out of nine children with hearing impairment are benefited. They believe that this type of surgery remains a highly beneficial procedure in selected cases. Morrison [3] stated that "hyperplasia of the adenoids is the chief source of ear infections in children."

On the other hand, Brown [4] concluded from a review of selected literature that "adenoids should seldom be removed. Occlusion of the nasopharynx constitutes the main indication for adenoidectomy; such occlusion is uncommon. Removal of the adenoids is not often likely to aid deafness, recurring otitis media and mastoiditis. There is evidence that adenoidectomy may aggravate these conditions since they are dependent largely on sinusitis." Brown also cited Lemere, Lewis, and Grover and Welsh to the effect that deafness almost invariably continues following adenoidectomy and that the incidence of recurrent otitis media is not lessened by this procedure. McAuliffe [5] stated that "it is no uncommon thing to see children suffering from otitis and nasopharyngeal inflammation after a thorough exenteration of lymphoid masses."

Conductive hearing loss is rather common in children. Of 35,000 Chicago Public School children,[6] 2.8% showed a loss of 30 db. or more in two or more test frequencies. Landis [7] reported that 4% of children in the Philadelphia school system had impaired hearing and that 80% of these losses were conductive in nature.

Such marked differences of opinion concerning the effectiveness of adenoidectomy in dealing with this problem indicate a need for reappraisal based on objective audiometric studies. The purpose of this study is to determine the role of hypertrophied adenoids in children with conductive deafness by obtaining reliable pre- and postoperative audiograms.

## Materials and Methods

One hundred consecutively seen children, 3 to 14 years of age, were studied. These had been referred to one of us (J. S.) because of signs and symptoms referable to the ears and their condition fulfilled the following criteria: presence of hypertrophied adenoid tissue; presence of stabilized, measurable conductive deafness as evidenced by a hearing loss of at least 15 db. in two or more frequencies in the same ear, and failure of conservative therapy (including antibiotics, local treatments, and, in some instances, irradiation with radium and x-ray) to resolve the patients' symptoms. Following adenoidectomy, which in many cases was a revision of a previous operation, the patients were examined at varying intervals. As a rule, audiograms were performed at each examination.

The history included information concerning the nature and frequency of ear infections, deafness, mouth breathing, allergic symptoms, earlier adenoidectomy, and previous treatment.

The ears, nose, and throat were examined visually. The nasopharynx was examined by digital palpa-

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tion and, in most cases (even in young children), by direct visualization through a nasopharyngoscope.

All hearing studies were made by one of us (J. S.) and a skilled technician, using calibrated equipment, in a sound-proof room in which the noise level was well below the maximum permissible for testing normal hearing. Test equipment included a 7BP Audivox pure-tone audiometer and a custom-built hearing evaluator which measures loss for speech rather than for pure tones. In several instances a psychogalvanic skin resistance apparatus was used to establish or confirm a hearing threshold.

At least two independent thresholds for hearing were obtained with each patient, and additional audiograms were made when inconsistencies were found. In many cases the resulting pure-tone tests were confirmed by speech-reception tests with ear phones.

Every possible effort was made to obtain hearing thresholds that represented relatively stable hearing situations rather than temporary hearing loss attributable to acute infection or allergy. In children with acute otitis media or otorrhea audiograms were taken only after inflammation and otorrhea had subsided.

All hearing losses in this study were judged to be conductive in nature on the basis of findings in audiograms, bone-conduction tests, speech-discrimination tests (in some instances), tuning-fork tests, and physical findings.

Despite the fact that many of the children had been treated by the referring physicians over long periods, conservative therapy was often continued, sometimes for as long as two years. These hundred adenoidectomies represent, as a group, operations performed on children who had not responded adequately to conservative therapy.

The number of preoperative audiograms per patient varied widely. Only the last of these for each patient was considered in this study. While every effort was made to obtain presumably stable thresholds, it is doubtless true that at various times the children had somewhat better or worse thresholds than were measured at the last visit before the operation. Such variation is inherent in a study of this nature. In any event, the last preoperative audiogram was not consistently the best or the worst of the preoperative tests and seems to offer an acceptable baseline against which to compare postoperative findings.

For each child at least one postoperative audiogram was performed, in the same manner as preoperatively. With 78 of these, the first postoperative audiogram was performed within two weeks; with 88, within one month. Most children had more than a single postoperative audiogram. Some were followed for several years. In every case the following postoperative audiograms, when available, were used for this study: (1) the last audiogram at two weeks or less postoperatively, (2) the last audiogram more than two weeks to one month postoperatively, (3) the last audiogram more than one month to six months postoperatively, (4) the last audiogram more than six months postoperatively.

Hearing was tested at 250, 500, 1000, 2000, 4000, and 8000 cps, but the lowest and the highest frequencies are not included in this report.

## Results

Preoperatively, 99 of the 100 children showed evidence of abnormal tympanic membranes, 91 had enlarged cervical nodes, and 83 had histories of being "hard of hearing"; 82 had histories of attacks of otitis media, and 77 were mouth breathers. Every child exhibited at least three of these conditions; 34 had four conditions, and 49 had all five.

It is of interest to note that 38 patients included in this study had had a previous tonsillectomy and adenoidectomy before being referred to one of us (J. S.). In these cases a revision of the adenoidectomy was performed. There were no appreciable differences between those with and those without previous tonsillectomies and adenoidectomies with respect to either preoperative findings or outcome of the present adenoidectomy. The two groups, therefore, are not shown separately. Since four frequencies were used in testing, the following arbitrary criteria were established to compare the postoperative with the preoperative findings.

Cured. The hearing difficulty was deemed "cured" if there was no loss greater than 5 db. at any two frequencies in either ear and no loss greater than 15 db. in any single frequency in either ear. In addition, there had to be an improvement of at least 10 db. in two or more frequencies in the same ear.

Improved. This indicated a significant improvement in hearing which had not, however, reached a completely normal level (more specifically, an improvement of 10 db. or more in at least two frequencies in the same ear, no increase in loss greater than 10 db. at any frequency, and no more than one increase as large as 10 db.).

*Hearing Status of One Hundred Children at Various Intervals After Adenoidectomy*

| Hearing Status * | Per Cent of Children Tested | | | |
|---|---|---|---|---|
| | Time After Operation | | | |
| | 2 Wk. or Less | Over 2 Wk. to 1 Mo. | Over 1 Mo. to 6 Mo. | Over 6 Mo. |
| "Cured" | 40 | 63 | 49 | 50 |
| Improved | 42 | 34 | 47 | 46 |
| No change | 9 | 3 | 2 | 4 |
| Worse | 9 | 0 | 2 | 0 |
| Total | 100 | 100 | 100 | 100 |
| | 78 (children) | 32 (children) | 41 (children) | 26 (children) |

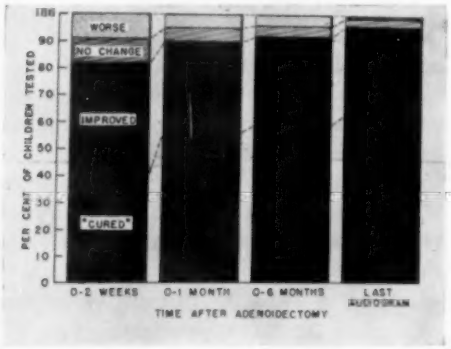
* In comparison with preoperative status.

Worse. This indicated an increase in loss of 10 db. or more in two or more frequencies in the same ear.

No change. All other cases.

The hearing status of these children following adenoidectomy is presented in the Table and in Figure 1. In the Table, data are presented for various intervals after operation. In Figure 1 the intervals are cumulated to give last-known status as of operation to two weeks, operation to one month, operation to six months, and, finally, last-known status regardless of time elapsed. Thus, percentages in Figure 1 are based on 78 children tested within the first two weeks, on 88 children tested within the first month, on 96 tested within six months, and, finally, on all 100 children. Of the group, 26 children were followed for more than six months after adenoidectomy, 26 were followed between one and six months, 16 were not seen again after the first month, and 32 were examined for the last time within two weeks of adenoidectomy.

Fig. 1.—Hearing status of 100 children at cumulative intervals after adenoidectomy.




It is apparent from inspection of Figure 1 that the great majority had better hearing postoperatively than preoperatively. Within the first two weeks 40% of those tested could be considered cured; at the last visit this proportion increased to 63%. Within the first two weeks 82% were either cured or improved; at the last visit 96% were either cured or improved. Only one child was considered worse at the last visit, but this boy was seen within two weeks after operation and never returned for reexamination. Of the three children who showed no change, two were not seen after the first two weeks. Of 68 children followed for more than two weeks, none could be considered worse and only 1 showed no change; the rest were all either cured or improved.

In order to illustrate the magnitude of the postoperative changes, Figure 2 presents pre- and postoperative hearing loss in decibels at the time of the last available audiogram for each of the 100 children at 1000 cps. It seems obvious from inspection of the Figure that the declines in hearing loss were both consistent and substantial. For example, of those whose loss became zero, 3 had started with a loss of 10 db.; 8, with a loss of 15 db.; 10, with a loss of 20 db.; 5, with a loss of 25 db., and 28, with losses from 30 to 45 db.

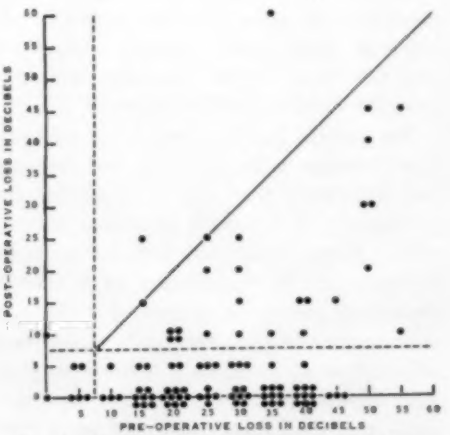



Fig. 2.—Hearing loss at 1000 cps in 100 children before and after adenoidectomy.

Of the 100 children, 6 had normal hearing at 1000 cps both before and after the operation. There were, however, 67 children whose hearing returned to normal and an additional 22 whose hearing, while not returning to normal, showed improvement. Two children had the same loss both before and after operation, and only three children showed a greater loss postoperatively.

## Comment

Since audiograms are not performed routinely on children, hearing loss is probably much more prevalent than is commonly believed. Children are usually spoken to in a raised voice, and losses are seldom noted until they approach 30 db. These losses occur insidiously in many children and may be present for months or even years before they are distinguished from mere childhood inattention. Adenoidectomies are often performed because of mouth breathing or chronic ear infection without preoperative audiograms; it seems reasonable to speculate that routine audiograms might reveal a substantial number of hearing losses in such children. In uncomplicated cases, hearing loss may subside under either conservative or surgical treatment without its existence ever having been noted by either parents or physicians.

Routine audiograms seem clearly indicated for all children with recurrent attacks of otitis media, chronic inattention and history of mouth breathing, and earache due to hypertrophied adenoids.

The present investigation of the relationship between adenoidectomy and hearing loss admittedly does not meet all the requirements of a rigidly controlled experiment. In particular, any conclusions must be tempered by the absence of a control group. It might be argued that the observed cures and improvements would have taken place spontaneously without surgical intervention. However, it seems most unlikely that the proportion would be as high as 56% cures and an additional 34% improvements within one month after the operation. Several children who had had marked and consistent hearing losses despite medical treatment for as long as two years suddenly achieved normal hearing in as little as one week after adenoidectomy. It would seem to be stretching coincidence too far to attribute this to anything but the adenoidectomy.

It is noteworthy that, except for eight children who required antibiotics over several days for a concurrent infection, no postoperative medication was used in this series.

The 38 patients with previous tonsillectomies and adenoidectomies, whose hearing loss and ear symptoms either persisted or recurred, are of particular interest. At surgery, all these children were found to possess considerable adenoid tissue, particularly behind the Eustachian tubes. In six instances the tip of one or both Eustachian tubes had been amputated during previous adenoidectomy. In 10 instances there was an extensive amount of scar tissue which bound the Eustachian tube to the postpharyngeal wall and blocked the orifice. In many cases only the lower portion of the adenoid mass appeared to have been removed in the previous surgery.

In the operations performed in the present group of cases, as much of the visible adenoid tissue as possible was removed under direct view, with particular attention to the areas surrounding both Eustachian tubes. The soft palate was retracted with special instruments so that the openings to the Eustachian tubes and the surrounding area could be clearly visualized. In revisions of previous adenoidectomies care was taken to remove not only the lymphoid tissue behind the Eustachian tubes but the scar tissue in this area as well. The lymphoid tissue was removed with an upturned punch in instances where it extended up to the posterior choanae. Extreme caution was exercised to avoid injuring the underlying tissue and the Eustachian tubes.

**Summary and Conclusions**

Adenoidectomies were performed on 100 children suffering from various degrees of conductive deafness. In every case conservative therapy, including antibiotics, local treatments, and, in some instances, irradiation with radium and x-ray, had failed.

After operation, of 78 children tested within two weeks, 40% were cured of their hearing loss and an additional 42% were improved. At the time of the last audiogram taken on all 100 patients, 63 were cured and 33 were improved; 3 showed no change, and only 1 could be considered worse.

Despite the absence of a control group, the proportion of cures and improvements seems considerably higher than could be explained on the basis of spontaneous resolution. It is concluded, therefore, that when conductive deafness, in a child with adenoid tissue, does not respond properly to conservative therapy, an adenoidectomy can often lead either to cure or to substantial improvement.

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Case Reports

# Promazine Modification of Reflex Rigidity in a Decerebrate Child

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The subcortical depressants, especially the phenothiazine derivatives, appear to possess a multiplicity of pharmacological properties and have been used in a variety of clinical disturbances.[1-3] From the body of pharmacological evidence accumulated, it is fairly apparent that certain of these compounds block the afferent pathways to the reticular area and exert a selective influence primarily on the diencephalon.[4,5]

A 19-month-old girl was admitted to the Babies' Hospital-Coit Memorial, Newark, N. J., at 12:45 a. m., on Feb. 7, 1956, in status epilepticus. She had had an elevation of temperature of mild degree, diarrhea, and vomiting and she had refused all liquids and taken no food for two days. Two weeks previously a similar episode, lasting two days, had occurred. She started to have generalized convulsions just prior to hospitalization and continued to convulse for several hours after admission. On cessation of the seizures the patient remained in a comatose state, followed in several days by a condition of wakeful decerebrate spasticity. The spasticity and wakefulness were alleviated by promazine.*

The family history was noncontributory. Spontaneous delivery had followed normal labor at term. Growth and development were normal. Routine immunizations had been performed; the child had received a satisfactory diet.

On physical examination after admission and cessation of the convulsions, the patient was cyanotic and in shock, with no response to painful stimuli. Extensive laboratory studies and repeated spinal fluid examinations failed to indicate the cause of the cerebral symptoms. The spinal fluid never showed any increase of cells or protein. During the first two weeks of hospitalization there was a general onset of reflex spasticity, with no return of awareness.

Accessory clinical findings on Feb. 7, 1956, the day of admission, included RBC, 3,750,000; Hb., 69%, 10 gm.; WBC, 4300, with 59% segmented forms, 39% lymphocytes, and 2% monocytes; CSF, cells, 2 lymphocytes, protein 10 mg., sugar 119 mg. On Feb. 9, 1956, findings were CSF, no cells; protein, 10 mg.; sugar, 105 mg. On Feb. 10, 1956, CSF, cells, 2 lymphocytes; protein, 6.5 mg.; sugar, 77 mg.

I was called in neurological consultation on the 17th hospital day. The child, exhausted and extremely emaciated, lay on her back in a posture of mild opisthotonic extension with severe carpopedal spasm, the toes pointing downward. Her eyes were conjugate and staring, with pupils dilated but reactive to light. The upper extremities were moderately flexed and semipronated at the elbows and severely flexed in tonic grip at the wrists and metacarpophalangeal joints. The fingers could not be extended with force. Arrhythmic flexion at each hip and knee fleetingly interrupted the tonic extension so that the heels would intermittently rub the bed sheets. Respirations were rapid (40 to 60 per minute). The mouth made constant disorganized champing movements capable of cutting rubber tubing. Nourishment was given by intravenous infusion, as the swallowing mechanism did not function. The child continually uttered unnatural, mechanical cries. Perspiration occurred at irregular intervals, as though diencephalic centers were discharged intermittently. It was thought that the continuous jaw and limb movements were caused by disturbance of basal ganglionic control and that some of the carpopedal spasm might be the result of a tetanic state from a centrally determined hyperpnea superimposed on the decerebrate spastic posture.

Whether failure of cortical function occurred as a result of ictal exhaustion or of actual tissue destruction with cell death was, at first, undeterminable. Ictal exhaustion would be expected to be followed by com-

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From the Babies' Hospital-Coit Memorial, Newark, N. J.

*Available as Sparine Hydrochloride (promazine hydrochloride, 10-[3-dimethylaminopropyl] phenothiazine hydrochloride) from Wyeth Laboratories.

plete recovery, as in Todd's paralysis.* The failure of recovery makes it obvious that neural tissue destruction occurred. The etiologic basis might have been one of the gross demyelinating disorders such as encephalitis periaxialis diffusa of Schilder,† but the fact that there have been no further recurrences in two years argues against this disease. Some type of cerebral anaphylaxis involving the large connecting pathways from cortex to the lower centers might be considered, with sensitization to a foreign agent occurring two weeks before a second invasion produced the shocking reaction, but the child had no known allergic tendencies. Various toxic and metabolic disorders involving the nervous system are considered among possible etiologic factors. These include disseminated encephalomyelitis or myelinoclasis following measles and other virus infections. As a rule, although this may be as catastrophic in onset, the end-result is not as devastating as in this case.‡ Acute toxic encephalopathy with primarily parenchymal cell changes accompanying acute and severe infections is manifest by delirium, stupor, and convulsions but results either in recovery with little or no residuals or in rapid death.§ Hemorrhagic encephalopathy is not easy to distinguish sharply from toxic encephalopathy.‖ This category comes closest to fitting the case presented here. As a rule the onset is abrupt and marked by high fever, convulsions, and coma. Muscular rigidity and bilateral Babinski signs are usually found. Bulbar symptoms may be present. If the patient survives, there may be spastic paraparesis with ataxia, difficulty in control of the bladder, reduction of cutaneous sensibility, and some mental changes. Almost all the acute infections, including influenza; pneumonia, especially virus pneumonia; scarlet fever; diphtheria; pertussis; typhus, typhoid fever, and malaria are among those frequently incriminated. Various exogenous poisons including arsenicals, carbon monoxide, and hydrocyanic acid as well as vitamin deficiency can cause this condition. However, no such noxious cause was present in this case. The patient had only a temperature elevation of mild degree, diarrhea, vomiting, and anorexia for two days, preceded two weeks previously by a similar episode lasting two days.

I believe that a toxic substance, probably a virus, competing for a necessary metabolite in the cell respiratory chemistry might produce any one of the above conditions and would destroy the cells closest to respiratory exhaustion first. In this case the long fibers of the descending cortical cells were most severely damaged, for these were subject to the exhaustion of repeated ictal discharge. Perhaps under the circumstances even the virus of the common cold might have precipitated the damage by competing for low reserves of vitamin B constituents such as thiamine (vitamin $B_1$), pyrodoxine (vitamin $B_6$) or cyanocobalamin (vitamin $B_{12}$).

Whatever the cause, the large connecting pathways from cortex to lower areas were rendered functionless. Diencephalic activity released from cortical control resulted in decerebrate spasticity, superimposed basal ganglia-type automatism, and continued wakefulness. Feeding and adequate nursing care were difficult. The immediate problem was to relieve the severe spastic quadriplegia and control the superimposed adventitious movements of limbs and jaws to prevent death by exhaustion and to facilitate gavage.

Following slow administration of 25 mg. of promazine hydrochloride by deep intramuscular injection over a period of five minutes, the limbs relaxed, the spasmodic movements ceased, and the eyes rolled up into the position of sleep. The cold moist pale skin of the face became warm, dry, and moderately flushed. The cry stopped, and respirations slowed to a normal rate. The fingers and wrists remained in severe flexion as a result of the muscle and tendon changes that had already taken place. Doses of 7.5 to 12.5 mg. of promazine were administered intramuscularly thereafter at four-hour intervals for two days to maintain control

* Reference 6, Chap. 6, p. 1034.
† Reference 6, p. 334.
‡ Reference 6, p. 615.
§ Reference 6, p. 654.
‖ Reference 6, p. 776.

of the severe extensor spasm, exhausting cry, and motor restlessness. After this time the patient appeared to be at a higher level of integration, in that she made more purposeful mouth movements (sucking). The flexion of fingers and wrists responded to passive stretching.

Electroencephalograms were taken after the start of medication (about three weeks after onset of the decerebrate state) with the child awake but drowsy, 12.5 mg. of promazine hydrochloride having been administered by intramuscular injection three hours previously. The tracings showed bilaterally symmetrical, relatively high amplitude, three- to four-per-second wave forms ordinarily associated with comatose states, increase in intracranial pressure, or postencephalitic conditions. Occasionally, relatively rapid activity replaced the slow-wave forms. The rapid activity was considered an indication of cerebrocortical electrical function. By the following week some 6- to 7-per-second activity was recorded in the electroencephalogram, which led to the impression of further return of cortical activity.

Oral administration of promazine was begun after three days of intramuscular administration. Four doses of 12.5 mg. of the fluid form of the drug were given daily by mouth, in liquids. After the morning dose of 12.5 mg. the patient would sometimes remain relaxed and quiet until mid-afternoon.

The patient was discharged on the 52d hospital day, after having been receiving medication with promazine for 35 days. Neurological examination showed a relaxed child who, having taken oral medication with promazine, was quiet, was able to make well-integrated mouth movements, and ate and swallowed well. She attempted to draw herself up on her knees if left on her stomach. Her glance did not follow a light, and she did not respond to the sound of even her mother's voice.

After discharge, maintenance doses of 7.5 mg. of promazine were administered orally in liquids three to four times daily for seven months. During this time there was some gradual return of higher integration, but not to the level at which natural rest became possible. She was capable of sleep only under the influence of promazine. In this period tonic seizures developed, lasting 40 to 45 seconds and occurring one to several times a day. In such attacks her head would turn partially to the right and her upper extremities would tend to extend outward and upward. The convulsions were controlled with ⅝ grain (about 40.6 mg.) of diphenylhydantoin daily. Promazine therapy was continued.

On Oct. 9, 1956, eight months after onset of the initial illness, the patient looked extremely bright. The unusual alertness and sparkling-eyed appearance of this child was in striking contrast to her demented state. She smiled in response to her parents' voices and to being held and fondled by them. Her mother would hold her most of the time. She ate well, and had begun to chew her food. She was still severely spastic but had some spontaneous movements of her hands. Deep tendon reflexes were overactive, and Babinski's sign was present bilaterally. The extensor spasticity had relaxed to such degree that she looked like a normal child when sitting on her mother's lap, but she became totally spastic if displeased or if placed alone on the floor.

When seen on Dec. 17, 1956, the patient followed the movements of others with her eyes and laughed if they smiled at her, as long as she was held by her mother. Reintegration of visual cognition was apparent. Cortical function discernible electroencephalographically on previous occasions now seemed to be available as a physiologic attribute to the psychobiologic unit. Administration of promazine had been stopped. Diphenylhydantoin therapy was continued in dosage of ⅝ grain daily, and phenobarbital was used for sedation at night. At earlier stages of disintegration the higher centers responsible for the suppressing action of sleep were not capable of overcoming the alerting reticular formation mechanism unless the incoming activating impulses to the reticular formation were attenuated by promazine.

The patient's parents moved to a remote town. By telephone they reported in June, 1957, that her recovery had progressed little since December, 1956. When placed on her back, the patient was still unable to turn over onto her stomach.

## Summary

Gross cerebral failure was initiated in a 19-month-old girl by convulsive phenomena following a mild gastrointestinal disorder. The over-all picture was that of a child in decerebrate condition, with release of diencephalic and brain-stem function resulting in continuous automatic activity and decerebrate spasticity. The central excitatory state was suppressed below the diencephalic level with promazine, in an initial dose of 25 mg. intramuscularly, followed by four intramuscular injections of 12.5 mg. per day for two days. The fluid form of the compound was then administered by mouth in the same dosage. After the patient's discharge from the hospital, maintenance doses of 7.5 mg. were administered orally. Reflex excitability was inhibited with proma-

zine. Decerebrate spasticity was relaxed. Mechanical crying was controlled. The child was enabled to sleep naturally, probably by attenuation of the impulses that had been stimulating the alerting mechanism in the reticular formation.

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# Spontaneous Thrombosis of the Internal Carotid Artery in a Seven-Year-Old Child

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Spontaneous thrombosis of the internal carotid artery is becoming recognized as one of the major causes of hemiplegia.[1,8-14,23] While there are many cases of thrombosis of the internal carotid artery secondary to direct trauma to the artery,[3,4,6,16,18,20] the incidence of spontaneous thrombosis in children without any antecedent trauma or underlying systemic pathology is rare. We have discovered in the literature [2,5,7,15,17,18,21] eight cases of thrombosis of the internal carotid artery in persons under the age of 20 years, six of which were verified by angiography or autopsy, but only one verified case of spontaneous thrombosis in a child less than 10 years old. This was in a 5-year-old boy reported by Shapiro.[21] Behrman [2] reports a case in a 7-year-old boy, but the diagnosis was made only by the presence of diminished pulsation of the carotid artery and was not verified by angiography. Clark and Linell [5] describe an occlusion of the internal carotid artery in a newborn infant with erythroblastosis fetalis, but this was presumed to be due to an embolus of infarcted necrotic placental tissue rather than a thrombosis (the patient had a patent foramen ovale and ductus arteriosus). The following case is believed to be the second verified case of spontaneous thrombosis of the internal carotid artery reported in the first decade of life.

## Report of Case

A 7-year-old white boy was admitted to the hospital on Jan. 7, 1956, with the history that one and one-half hours prior to admission, while playing, the patient suddenly complained of a headache and stated that he was going home. He started to get on his bicycle and fell off. He did not get up and could not talk. Shortly after this, he lost consciousness and was brought to the hospital, where examination revealed a semicomatose, cyanotic child whose respirations were 23 per minute, shallow and regular. His pulse rate was 58, and the blood pressure was 86/50. There was a partial right facial paralysis and incomplete weakness of the right upper and lower extremities. The radial and biceps reflexes were brisk and equal, but the right patellar and Achilles reflexes were somewhat diminished as compared with the left. There were suggestive bilateral Babinski signs. The cremasteric reflexes were present but more marked on the left than on the right. The abdominal reflexes were absent on the right and present on the left. The pupils were dilated, and the right pupil was larger than the left. Both reacted to light.

The past history revealed the child to be of normal birth and development, with no previous serious illnesses. The patient had had right otitis media two years previously, which was uncomplicated. He had had no recent accidents. The parents and one other sibling were all living and well.

Blood cell count on admission revealed 3,850,000 red blood cells, with 10.4 gm., or 67%, hemoglobin and a white blood cell count of 14,400, with 71% segmented cells, 22% lymphocytes, 1% eosinophils, and 1% basophils. Blood urea nitrogen was 12.4 mg. per 100 cc., and blood sugar was 134 mg. per 100 cc. Urinalysis was negative except for a very faint trace of albumin. A spinal puncture performed on admission revealed an initial pressure of 164 mm. of water, with clear, colorless fluid containing 2 white blood cells per cubic millimeter, no globulin, and a total protein of 37 mg. per 100 cc. Blood culture and spinal fluid culture revealed no growth.

One hour after the original examination there seemed to be an increase in the right flaccid paralysis. The patient was aphasic but was more alert. He responded to requests and grunted but could not speak. General physical examination at that time revealed nothing of note in the ears, nose, or throat. The lungs were clear. The heart tones were of good quality and slow, and there were no murmurs. The abdomen was semiscaphoid, with no abnormal masses. The liver and spleen

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were not enlarged. The genitalia and extremities were normal except for the right-sided paralysis.

On the following day the patient was definitely more alert. He could carry out simple commands and seemed rational and cooperative. He would not move his right upper or lower extremities upon command but would withdraw them from noxious stimuli. His pupils were equal. He was having seizures of the right upper extremity only, characterized by very slow (30 to 60 per minute) clonic contractions and not accompanied by unconsciousness. He was vomiting, but his blood pressure was stable around 100/60 and his pulse rate ranged between 90 and 100. Two days after admission the patient became more comatose and had an accumulation of secretions in the pharynx. The pupils were equal but reacted sluggishly to light, with slight rebound. The remainder of the neurologic findings persisted unchanged, with right hemiplegia and positive right Babinski sign. Spinal puncture was repeated and revealed an initial pressure of 140 mm. of water, with clear, colorless fluid containing 5 white blood cells per cubic millimeter and a total protein of 31 mg. per 100 cc. Because the patient's condition was becoming progressively worse, it was decided to perform immediate angiography. Under endotracheal anesthesia left percutaneous cerebral angiography was performed, revealing good filling of the common carotid artery and the external carotid artery, with filling of the first 3.5 cm. of the internal carotid artery. Beyond this point there was complete failure of the internal carotid artery or its branches to fill. Following angiography the patient's condition went rapidly downhill, and he died at 8 p. m. on Jan. 9, 1956.

*Autopsy.*—Autopsy revealed the left internal carotid artery to be completely thrombosed. The thrombosis extended into the anterior and middle cerebral arteries as well. There did not appear to be any collateral circulation from the ophthalmic artery or from the vessels on the opposite side through the circle of Willis. The intima of the internal carotid artery was not roughened, thickened, or scarred, and there were no obvious intra-arterial abnormalities to account for the thrombosis. Examination of the heart did not reveal any endocardial abnormalities. The remainder of the examination was normal.

Left percutaneous carotid arteriogram, showing complete occlusion of the internal carotid artery 3.5 cm. above its origin.

*Goldstein—Burgess*

## Comment

Spontaneous thrombosis of the internal carotid artery in the neck is primarily a disease of middle life, but cases in younger persons have been reported. The mechanism of the causation of the thrombosis is obscure. It occurs in the course of debilitating disease, and occasionally endocarditis is a causative factor. Gurdjian and Webster [11] suggest that the thrombosis appears to result from the operation of insidious factors producing atheromatous degenerations in the blood vessels. Occasionally an aneurysmal dilatation may occlude the artery by kinking the vessel. Hypertension and syphilis appear to be of little importance. None of these factors seems to play a part in this case, and the cause of the sudden thrombosis in this previously healthy and active child remains a mystery.

The importance of the establishment of adequate collateral circulation by way of the ophthalmic artery has been demonstrated [13, 21,22] in cases in which the patients subsequently recovered. In this case we were unable to demonstrate any evidence of collateral circulation, and this is undoubtedly the reason for the fatal outcome. This is borne out by the complete occlusion of the anterior and middle cerebral arteries as well as the internal carotid.

## Summary

A case of fatal spontaneous thrombosis of the internal carotid artery is presented

in a 7-year-old boy who was previously healthy and active. No causative factor could be found. There is believed to be only one other similar case reported in the first decade of life.

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Progress in Pediatrics

# Etiologic Factors in Mental Deficiency

*Errors of Metabolism That May Lead to Mental Deficiency*

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## Introduction

In certain mental deficiencies an association has been established between the mental defect and a genetically determined biochemical abnormality. For instance, in the phenylketonuric person there is a specific biochemical defect, with the mode of inheritance well known; in others, e. g., the Mongoloid patient, a biochemical defect may be present and the question of inheritance is still debated. Though patients with known biochemical defects constitute only a small portion of all the mental defectives, the number of specific syndromes identified is increasing as the result of continuing research. This rapidly expanding knowledge warrants a summary, with a hope that it will stimulate clinical search for additional patients and entities.

In those conditions where the biochemical abnormality is well understood, the basic mechanism is a genetically determined defect in enzyme function, which manifests itself in deviant metabolism of a specific nutrient or substrate. Our classification is in accordance with the major metabolic substance involved, e. g., diseases of protein, carbohydrate, and lipid metabolism. Diseases of hormone synthesis and conditions where the biochemical background is less clearly defined are discussed separately. Extensive reviews on all of these conditions are available elsewhere.[1-4,20,23,36,53,71,130]

It should be remembered that, since enzymes are proteins, all diseases described in this paper may properly be called "protein diseases." For easier understanding, however, they are grouped in accordance with the substrate involved in the specific enzymatic process. To avoid a twofold meaning of "protein disease," we suggest the general term "enzymatic mental defects."

## Disorders of Protein Metabolism

The important clinical, metabolic, and genetic aspects of mental defects with disorders of protein metabolism are tabulated in Table 1. Phenylketonuria may well be viewed as a model disease for metabolic research. The clinical findings and certain aspects of this metabolic abnormality are well defined. The pattern of inheritance is clearly understood. There are indications that the heterozygote can be identified by laboratory tests, and at least one type of rational treatment is known. H disease is a recently described entity involving tryptophan metabolism. Research in hepatolenticular degeneration has resulted in a better understanding of copper metabolism.

*Phenylketonuria.*—Phenylketonuria (phenylpyruvic oligophrenia) is a metabolic disturbance characterized by an almost complete failure to hydroxylate phenylalanine, an essential amino acid, to tyrosine.[3,4] Usually

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TABLE 1.—*Mental Defects with Disorders of Protein Metabolism*

| Disease | Clinical Findings | Metabolic Abnormalities | | Genetics | |
|---|---|---|---|---|---|
| | | Primary | Secondary | Inheritance | Abnormality in Heterozygote |
| Phenylketonuria | Mental deficiency, blonde hair, blue eyes, fair skin, eczema, musty odor of urine [2, 4, 24] | Absent phenylalanine hydroxylase activity [11-13] | Incr. serum phenylalanine, incr. urine phenylalanine and derivatives -pyruvic, -lactic, -acetic acids [3, 9, 19] | Recessive [4] | Decr. tolerance to ingestion of phenyl alanine [7] |
| H disease | Mental deterioration, pellagra-like rash, cerebellar ataxia, photosensitivity [21] | Tryptophan (?) [21] | Incr. urine tryptophan indoleacetic, indoleacetylglutamine, and indican; aminoaciduria [21] | Recessive (?) [21] | Unknown [21] |
| Hepatolenticular degeneration | Mental deterioration, neurological signs, cirrhosis, pigmented ring at limbus of cornea [22] | Decr. synthesis of ceruloplasmin (?); synthesis of proteins with incr. affinity for copper (?) [23, 24, 25] | Decr. serum ceruloplasmin and copper; incr. urine copper; amino-aciduria; excess deposition of copper in tissues [12-25] | Recessive [23] | Unknown [23] |

severe mental deficiency is present. Abnormal behavior patterns and seizures are frequent.[4,5] In most patients the hair is blonde, the eyes are blue, and the skin is fair. Eczema is often a prominent feature in infancy. Several phenylalanine derivatives appear in the urine. Phenylpyruvic acid is excreted in large quantities and can be detected by a characteristic color when ferric chloride is added or a precipitate when dinitrophenylhydrazine is added to the urine. Another derivative, phenylacetic acid, lends to the urine a strong musty or aromatic odor. The urine tests are simple and, when positive, are diagnostic of phenylketonuria.

The disorder is transmitted as a non-sex-linked Mendelian recessive trait and occurs about once in 25,000 births.[6] Consanguineous marriages had occurred in about 10% of the affected families. Some 350 cases have been reported in the literature, mostly from institutions for the mentally deficient.[3] Milder degrees of mental defect may have escaped detection.

Few neuropathological changes have been reported, despite the severity of the mental defect. Although the brain is of normal size, the convolutional pattern resembles that of a newborn infant, suggesting a developmental inhibition during early postnatal life. Defects in myelination, as well as cortical atrophy, have been reported,[8] but some investigators found no changes. The other organs are anatomically normal.

The biochemical disturbance becomes evident shortly after birth. Phenylalanine is not *p*-hydroxylated to form tyrosine; thus, it accumulates in the body and is excreted in the urine, together with its derivatives, phenylpyruvic, phenyllactic, and phenylacetic acids.[3,4,19] The latter is conjugated with glutamine to form phenylacetylglutamine. Glutamine, glutamic acid, and aspartic acid, serving as amino donors, may temporarily decrease the urinary excretion of phenyl, pyruvic, and lactic acids.[18] An alternate pathway for hydroxylation of phenylalanine is through the formation of *o*-hydroxyphenylalanine (*o*-tyrosine) and thence to *o*-hydroxyphenylacetic acid, which is excreted in excess amounts.[9] The severity of the mental defect has not been correlated with the quantities of phenyl compounds excreted or found in the body tissues.[3] Deficiencies in thyroid and adrenal function do not occur, despite the inbility of the phenylketonuric patient to form tyrosine.[3,132] It has been demonstrated in vitro that an excess of phenylalanine inhibits the conversion of tyrosine to melanin,[10] a fact which may account for the fair complexion of the patients.

An enzyme, phenylalanine hydroxylase, is responsible for the normal *p*-hydroxylation of phenylalanine to tyrosine. The enzyme consists of two protein fractions, one of which is present in many tissues, including

the brain. The other is found only in the liver and is absent in the phenylketonuric person.[11-13]

Interest has been directed recently toward the treatment of this disorder with low-phenylalanine diets,[14-16] usually consisting of an acid hydrolysate of casein with phenylalanine removed, supplemented with additional amino acids, minerals, and choline. Carbohydrate and fat are added to meet caloric requirements. The phenylalanine-free hydrolysate is administered for several weeks until the serum phenylalanine falls to a normal range, after which small amounts of protein are added to supply 15 to 20 mg. of phenylalanine per kilogram per day. The average daily requirement for normal children has been estimated between 80 and 200 mg. per kilogram per day.

The biochemical response to this diet is striking; the serum phenylalanine falls to normal values and the phenyl derivatives disappear from the urine.[17] Clinically, the response is more variable and depends upon the age at which treatment is initiated. One infant, started on the diet at 7 weeks of age, is reported to be developing normally at 2 years.[16] In older children improvement in attention span, in behavior, and in the electroencephalographic pattern has been reported by some authors.[5,14,16] Others question the clinical benefits obtained from the diet in older patients. Unpalatability, gastrointestinal disturbances, weight loss, anemia, and malnutrition may significantly complicate the administration of the diet. It is not known how long this treatment must be continued, and it should not be used in nonphenylketonuric mental defectives.

Considerable progress has been made in the past decade toward understanding this disorder.[20] The demonstration of such features as a single gene defect, the inactivity of a specific enzyme system, the demonstration of multiple metabolic abnormalities, and the development of a rational therapy are highlights of this progress. If confirmed, the detection of the heterozygote by means of decreased tolerance to ingestion of phenylalanine would make it possible to give more adequate genetic counsel to families.[7] Much remains to be learned, however, about the cause of the mental defect and the ultimate value of the low-phenylalanine diet.

*H Disease.*—A disorder of tryptophan metabolism was described by a group of English investigators in 1956 under the title "Hereditary Pellagra-like Skin Rash with Temporary Cerebellar Ataxia, Constant Amino-Aciduria, and Other Bizarre Biochemical Features."[21] It involved four of eight children in a family in which the parents were first cousins. The name H disease was suggested by the initial of the family. It is now known that other patients with the disease have been mistakenly diagnosed as having pellagra.[21,22]

A symptom noted in late childhood or adolescence was a dry red scaly rash on the exposed surfaces of the body. The rash was similar to that seen in pellagra, but there were no changes on the oral mucosa or the tongue. During the acute phase of the rash, fever, cerebellar disturbance with ataxia, diplopia, and nystagmus were present. All clinical symptoms with the exception of the mental defect were reversible. Psychological testing revealed a mild degree of mental defect, with slow but progressive deterioration.

Biochemical studies showed a renal aminoaciduria and abnormalities in indole metabolism. A block in the conversion of tryptophan to kynurenic or nicotinic acid was suggested as the basic defect, resulting in an increased excretion of tryptophan and other indole compounds, such as indoleacetic acid, indoleacetylglutamine, and indican. The pattern of amino acids excreted in the urine is believed to be specific for this disease, and all patients showed the same pattern. A similarity to the metabolic defect in phenylketonuria has been suggested; however, the pyruvic and lactic acid derivatives of tryptophan have not been described in the urine.

The clinical picture was characterized by acute exacerbations superimposed on the



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chronic course. The exacerbations were triggered by exogenous factors such as exposure to sunlight, dietary deficiencies, and infection. Under these conditions the body's demand for nicotinic acid may have increased, thus precipitating the clinical features of the disease. This suggestion was supported by the partial benefit from nicotinamide administration in the treatment of the acute phase of the disease.

*Hepatolenticular Degeneration (Wilson's Disease).*—The biochemical abnormalities in hepatolenticular degeneration are thought to be the result of the synthesis of tissue proteins which have an increased affinity for copper. The defective synthesis of a copper-binding globulin, ceruloplasmin, may explain the pathology in a different way. In either case, excessive amounts of copper are deposited in the brain, liver, kidneys, and other organs.

The clinical onset of the disease is usually in adolescence; signs of basal ganglia involvement with tremor, rigidity, dysarthria, and mental deterioration predominate.[23] A ring of brownish or greenish pigmentation at the limbus of the cornea, the Kayser-Fleischer ring, is almost always present and is pathognomonic of the disease. Cirrhosis may be evident only in tests of hepatic function, though in a few patients, particularly in adolescents, it may be the presenting complaint. Roentgenologic studies reveal degenerative changes and fragmentation of the bones about the joints, with osteoporosis and occasional fractures.[23]

The biochemical defect affects the metabolism of copper. The serum copper is decreased, and the urinary excretion of copper is increased. The pathogenesis of the disorder is not firmly established. One concept suggests that a genetic defect leads to the formation of proteins having a high affinity for copper; hence excessive deposition of copper within the tissues.[32] A second concept suggests that the basic defect is a decreased synthesis of ceruloplasmin, a copper-containing serum globulin.[23,25,26] The significance of the decrease in this protein, which acts as an oxidase in vitro, is not known. Isotope studies with $Cu^{64}$ in these patients indicate an increased absorption from the intestinal tract, but the copper remains bound to albumin and fails to be incorporated into ceruloplasmin.[27] Copper, not bound to ceruloplasmin, is then excreted in the urine or deposited within the tissues of several organs, among them the basal ganglia, the cerebral cortex, the cornea, the liver, and the kidney. The copper deposition leads to the development of symptoms. Renal abnormalities, including amino-aciduria of renal origin, as well as peptiduria, glycosuria, phosphaturia, proteinuria, and uricosuria have been described.[23,28,29] Evidence of both glomerular and tubular dysfunction has been presented.

A recessive mode of inheritance has been suggested because of the high rate of consanguinity and familial occurrence of the disease. A biochemical abnormality suggesting the heterozygous state has been found in only one patient.[23]

Treatment has been aimed at eliminating excess copper or preventing the absorption of copper from the bowel. In an effort to produce a negative copper balance dimercaprol (BAL; 2,3-dimercaptopropanol) and edathamil (Versene; ethylenediaminetetraacetic acid) were used. Penicillamine ($\beta,\beta$-dimethyl cysteine) has recently been introduced as a more effective agent.[31] The effect of estrogen has also been investigated.[23] Clinical success may depend upon the duration and the severity of the disease.

### Disorders of Carbohydrate Metabolism

Galactosemia is the best understood entity in this group. Its essential characteristics, together with those of idiopathic hypoglycemia, sucrosuria, and gargoylism, are listed in Table 2. The major metabolic substance involved in the first three is a relatively simple carbohydrate; in gargoylism it is a more complicated substance, most likely a mucopolysaccharide.

Idiopathic hypoglycemia may prove to be a disease of protein metabolism or an ab-

TABLE 2.—*Mental Defects with Disorders of Carbohydrate Metabolism*

| Disease | Clinical Findings | Metabolic Abnormalities | | Genetics | |
|---|---|---|---|---|---|
| | | Primary | Secondary | Inheritance | Abnormality in Heterozygote |
| Galactosemia | Mental deficiency, jaundice, hepatomegaly, cataracts [33, 34, 36] | Absent phosphogalactose uridyl transferase activity (PGal transferase) [36-42] | Incr. serum galactose; incr. urine galactose; amino-aciduria; accumulation of galactose-1-$PO_4$ in tissues [36, 38, 39, 44] | Recessive (?) [33] | Abnormal galactose-tolerance test in one or both parents (?) [36] |
| Idiopathic hypoglycemia | Mental deficiency, "blank" spells, seizures [45] | Unknown | Decr. blood glucose; casein- leucine-induced hypoglycemia [45, 46] | Unknown | Abnormal epinephrine and insulin sensitivity tests in one parent (?) [45, 47] |
| Sucrosuria | Mental defect, hiatus hernia [48] | Unknown | Sucrosuria [48] | Unknown | No studies |
| Gargoylism | Mental deficiency, coarse facial features, contractures, hepatosplenomegaly, corneal infiltration, skeletal deformities [49-51] | Mucopolysaccharides (?) [51, 52] | Incr. tissue polysaccharides; incr. urine chondroitin sulfuric acid [51, 52] | Recessive or sex-linked [49-51] | Unknown |

normality of hormone synthesis. The important role of at least two amino acids has been identified, though the basic defect remains unknown.

Proper classification of gargoylism is also debatable. It is identified with disorders of carbohydrate metabolism because present evidence suggests that the storage material is a mucopolysaccharide.

*Galactosemia.*—Galactosemia is a rare familial disturbance of carbohydrate metabolism characterized by an inability to utilize galactose.[33,34,36] The symptoms appear within a few weeks after birth and are precipitated by the ingestion of milk. Lactose, on hydrolysis, yields galactose and glucose. Jaundice, hepatomegaly, malnutrition, cataracts, neurological abnormalities, and mental deficiency result from the accumulation of galactose or the products of its intermediary metabolism. Large amounts of galactose are excreted in the urine, resulting in a positive Benedict reaction.* It may be accurately identified by appropriate chemical tests or chromatographic techniques.[37] The galactose-tolerance test is grossly abnormal, with a rapid rise and prolonged elevation of the blood galactose.[33-37] Proteinuria and amino-aciduria are present and may be increased by the tolerance test.[38] Liver-function tests are frequently abnormal.

The pathologic changes include fatty infiltration, cellular degeneration, and necrosis of the liver in the early stages[33-36]; Laennec's cirrhosis has been described in the later stages. Other findings include lamellar or nuclear cataracts and swelling of the renal tubular epithelium.[35] There are no reports of neuropathological findings.

Diagnosed cases are apparently rare; many infants may have died without correct diagnosis. Untreated patients usually die in infancy; some have survived, suggesting the possibility that there are mild forms of the disease, with alternate pathways developing for the metabolism of galactose.

The familial occurrence of the disease and the increased frequency of consanguineous marriages suggest a simple recessive genetic pattern of inheritance. The exact mechanism is as yet unknown. The heterozygous state has not been demonstrated with certainty by galactose-tolerance tests or by enzyme studies.[36,40]

Cellular metabolism in the galactosemic person has been the subject of intensive study in the past several years.[36,39-44] An accumulation of galactose-1-phosphate was first noted in the red cells of these patients, and it was suggested that large amounts of this substance in the lens, brain, liver, and kidney of galactosemic patients interfere

* Commercially prepared paper strips impregnated with glucose oxidase will give a negative reaction with urine containing galactose. Hence, it is important that the urine always be tested routinely with Benedict's reagent; otherwise the galactose may be missed.

with metabolic processes.[39] Recently it has been shown that galactose-1-phosphate competes for phosphoglucomutase and inhibits its phosphorylating activity, thus leading to a breakdown of normal cellular metabolism.[44]

Other investigations have revealed an absence in the red blood cells of an enzyme, phosphogalactose-uridyl-transferase (PGal-transferase) which is responsible for the conversion of galactose-1-phosphate to glucose-1-phosphate.[40,41] Although this enzymatic defect is also found in the liver, an alternate metabolic pathway in that organ accounts for the conversion of small amounts of galactose to glucose-1-phosphate by a pyrophosphorylase enzyme.[42,43]

Treatment of the disorder by the elimination of milk or lactose from the diet and the substitution of non-lactose-containing feedings results in the disappearance of galactose from the blood and urine and a prompt reversal of the symptoms.[33-36] Unless it is far advanced, the liver damage is reversible and cataracts disappear. Normal growth is resumed. The mental deficiency has persisted in a few infants, in spite of early recognition and treatment.[36] The intolerance to galactose always remains, although a galactose-free diet is not necessary after the first several years and small amounts of lactose-containing foods may then be given without harm. Several features of this disorder, such as the genetic pattern and the identification of the carrier state, require further investigation.

*Idiopathic Hypoglycemia (Hypoglycemosis).*—The idiopathic form of infantile hypoglycemia is a familial disease often complicated by mental deficiency. Seizures, blank spells, or episodes of staring may mark the onset. There is a prompt response to glucose administration. Spontaneous recovery usually occurs, leaving, at times, severe mental deficiency as the only remaining clinical stigma.[45,46] A genetic basis has been suggested because of the familial occurrence of the disease.[47] Increased insulin sensitivity has been noted in one healthy parent of affected persons. Too few patients have been studied, however, and the exact genetic pattern remains unknown.

Laboratory studies reveal low blood sugar levels even between attacks and a rapid fall in glucose during an intravenous glucose-tolerance test. Epinephrine- and glucagon-tolerance tests have been found to be normal.[45] Histopathological changes in the pancreas are minimal; many patients showed no changes; in others an absence of $\alpha$-cells and hyperplasia of the islet cells were described.

It may be more proper to consider this condition a disease of protein metabolism, but it is classified among the diseases of carbohydrate metabolism in this paper because of the primary clinical manifestations. Abnormalities of amino acid metabolism may play an important role in its etiology.[48] Casein hydrolysates, as well as leucine or its metabolic intermediate, isovaleric acid, produced hypoglycemia and convulsions when fed to four patients with this disease. Normal persons, at the same dosage levels, showed no response. This evidence suggests that in hyperglycemic patients leucine or isovaleric acid acts by increasing the secretion of insulin; an increase in blood insulin was noted in two patients. These amino acids may also in some way enhance the effect of insulin upon the blood glucose. Other amino acids have not been tested as yet. That several forms of the disease may exist is suggested by the variability of the pancreatic pathology and the observation that some patients respond normally to casein, leucine, or isovaleric acid.

The mental deficiency may result from failure to rceognize and treat the condition early. It seems to be related to the episodes of hypoglycemia, though other diseases of infancy, also characterized by hypoglycemia, e. g., glycogen-storage disease, adrenocortical insufficiency, anterior pituitary insufficiency, and inanition, are rarely complicated by mental deficiency. A quantitative difference in blood sugar levels or the presence of an

unknown factor in idiopathic hypoglycemia may account for this variation.

The most effective treatment has been with corticotropin (ACTH) administered intramuscularly in small daily doses. This elevates the blood sugar; the seizures cease, and, if treatment is started early, mental deficiency is prevented. Not all patients respond to corticotropin, suggesting that the disease may have different etiologies. Treatment with alloxan was found ineffective, as well as dangerous.[49] Pancreatic resection is of value only if an adenoma (rare in infants and children) is present.

*Sucrosuria.*—Sucrosuria was described in 1954 by a group of English investigators who reported three children with severe mental defect, hiatus hernia, and large amounts of a disaccharide, sucrose, in their urine,[50] which was identified by chromatographic techniques. Numerous studies failed to reveal the cause for the sucrosuria, and it was presumed that the patients had an inability to split sucrose in the intestinal tract; hence, it was absorbed and excreted intact. Sucrose was not produced endogenously. Variation in the amounts of sucrose, as well as other sugars excreted, was also related to lactose ingestion, suggesting an association between the two disaccharides. The relation between this anomaly of carbohydrate absorption and utilization and the mental retardation is not known.[51]

*Gargoylism.*—Gargoylism is also known as Hurler's disease, Hurler-Pfaundler disease, dysostosis multiplex, and lipochondrodystrophy.[52,71] The unfortunate term gargoylism was suggested because of the resemblance of these patients to the figures on the Cathedral of Notre Dame in Paris.[53] It is a congenital familial "storage" disease with widespread involvement of the tissues. The exact nature of the storage substance is unknown. At one time it was believed to be a lipid. Recent evidence suggests that this substance is related to the metabolism of those mucopolysaccharides which form the ground substance of the connective tissue. Therefore, the disease is included among the disorders of carbohydrate metabolism.

The clinical picture is characterized by involvement of the central nervous system, the skeletal system, the connective tissue, and the viscera.[52,53,59,60,71] The onset of the disease is from late infancy to adolescence. Coarse, grotesque facies; high forehead; elongated skull; prominent supraorbital ridges; heavy eyebrows; flat nose, and thickened lips and tongue characterize the appearance of the patient. The involvement of the lumbar vertebrae produces a marked kyphosis. The corneae may be clear or cloudy. Cardiac murmurs, hepatomegaly, and splenomegaly are common symptoms. Contractures about the interphalangeal joints, elbows, hips, and knees lead to progressive disability. Mental deficiency, with progressive deterioration, is usually present.

Radiographs of the skeletal system reveal pathognomonic changes as early as in the newborn period.[54] They include increased diaphyseal diameters; obliquity, narrowing, and distortion of the epiphyseal plates; broadening, shortening, and pointing of the phalangeal bones; notching or wedging of the ventral surfaces of the vertebrae, and splaying of the bodies of the ribs. The sella turcica has an increased anteroposterior diameter.[53,54,71] No rational treatment is known; the disease progresses in a slow and insidious fashion. Death usually occurs before 20 years of age and is due to intercurrent infection or cardiac disease.[55] Modified forms (formes frustes) have been reported in mentally deficient persons in whom the other characteristic clinical features were absent or minimal.[56] Radiographic changes, however, were present and helped to establish the diagnosis.

The incidence of gargoylism is low, and the frequency of the disease is estimated at 1 in 50,000 births. About 200 cases have been reported in the literature.[71] Consanguineous marriages are frequent in the parents. The disease is transmitted in two ways: in a non-sex-linked recessive manner or in a sex-linked manner with only males

affected.[57,58] Corneal infiltration is characteristic only of the non-sex-linked form, where deafness is infrequent (5%). In the sex-linked form the cornea is usually clear but deafness is common (50%). These findings suggest that two forms of the disease may exist with subtle clinical differences.

The histopathology is characterized by deposition within the cells of a storage substance, with swelling, granulation, and vacuolation of the cytoplasm.[59-62] Numerous organs are involved, including the reticuloendothelial system, with the liver, spleen, bone marrow, and lymph nodes; the vascular system, with intimal proliferation and focal deposition of the storage material within the arteries and heart valves[55]; the central nervous system, with involvement of the glia and ganglion cells; connective tissue elements, including fibrocytes, chondrocytes, and osteocytes; and epithelial cells of the cornea, skin, and liver. A nonspecific granular staining of the leukocytes has been reported.[63] This histological appearance of the lesions in the nervous system may resemble those seen in the familial amauroses.[64]

The staining reactions are variable, and the storage material has been variously identified as a lipid, lipoprotein, or glycoprotein substance. Recent studies suggest that it is a mucopolysaccharide similar to chondroitin-sulfuric acid, which has also been found in increased amounts in the urine.[65,67] Staining reactions with periodic acid-Schiff stain, after fixation in lead acetate, are positive and show striking metachromasia. Two storage fractions have now been isolated; one is a sulfonated mucopolysaccharide, and the other, a glycolipid.[66] A similar histopathological picture has been produced experimentally in animals by the injection of macromolecular carbohydrates, such as methylcellulose.[52] Normal serum values have been found for sterol esters, neutral fats, phospholipids, fatty acids, cholesterol, and cerebrosides.[52]

The accumulation of an excess amount of mucopolysaccharides in this disease may represent a genetically determined enzyme disturbance which affects the metabolism of these substances. It has been suggested that the defect may lie either in the "binding of mucopolysaccharides to protein" or the abnormal synthesis of "structural polysaccharides."[65,66] The disorder suggests a congenital disturbance in the formation of connective tissue.

### Disorders of Lipid Metabolism

The cerebral lipoidoses are a group of rare familial disorders of lipid metabolism, characterized by the accumulation of a lipid-containing "storage material" in the cells of the body. Table 3 lists the diseases which constitute this group. They are the familial amauroses, Niemann-Pick disease, and Gaucher's disease; there is some overlapping between these entities. The lipid accumulation in the familial amauroses, though not well defined, is thought to be a ganglioside, containing neuraminic acid; in Niemann-Pick disease it is a sphingomyelin, and in Gaucher's disease it is a galacto- or glucocerebroside, kerasin. There are several reports indicating that other abnormalities

TABLE 3.—*Mental Defects with Disorders of Lipid Metabolism*

| Disease | Clinical Findings | Metabolic Abnormalities | | Genetics | |
|---|---|---|---|---|---|
| | | Primary | Secondary | Inheritance | Abnormality in Heterozygote |
| Infantile amauroses | Mental deterioration, severe neurological disturbances, "cherry-red" spot in macula [71] | Gangliosides (?) [71] | Incr. gangliosides in CNS [73, 74, 75] | Recessive [71] | Unknown |
| Niemann-Pick disease | Mental deterioration, hepatosplenomegaly, anemia [71] | Sphingomyelin (?) [76] | Incr. sphingomyelin in R. E. system; Niemann-Pick cells [71, 76] | Recessive [71] | Unknown |
| Gaucher's disease (infantile form) | Mental deterioration, hepatosplenomegaly [71] | Cerebroside (kerasin) (?) [71, 64] | Incr. cerebrosides in spleen; Gaucher cells [71, 64] | Dominant (?) [64] | Gaucher cells [64] |

of lipid metabolism may also produce disease states with similar clinical and pathological findings.[68,69]

Progress toward understanding the disorders of lipid metabolism has been hindered by the complex chemical nature of the storage substances and difficulties of isolation, analysis, and characterization by histochemical[70] or other techniques. Little is known as yet of the metabolic pathways of lipid synthesis or degradation or of the enzymes which control these reactions; nor is there any promising method of treatment for these disorders.

*Familial Amauroses.*—The group of cerebral lipoidoses called familial amauroses is described under several eponyms Depending on the age of onset, from infancy through childhood, it is called Tay-Sachs disease, Bielschowsky's disease, and Spielmeyer-Vogt disease.[71,76] The neuropathlogical findings in all three are very similar, and no biochemical differences are known between these entities, which differ in age of onset. All show a recessive pattern of inheritance.

The early infantile form, Tay-Sachs disease, is most frequently found in Jewish infants of eastern European origin.[72] It begins in early infancy with evidence of developmental retardation and visual failure. Blindness; neurological deterioration, first with hypotonicity and later with hypertonicity; seizures; and, finally, decerebrate rigidity develop. Death occurs during the second or third year of life. Ophthalmoscopic examination reveals a pathognomonic "cherry-red" spot in the macula; the degeneration of the retinal ganglion cells allows visualization of the red choroid. Similar findings have been reported also in Niemann-Pick disease.[71]

The late infantile form, Bielschowsky's disease, and the juvenile form, Spielmeyer-Vogt disease, have a similar course, though the onset is later in life and the regression is slower. The infant or child appears normal until progressive visual failure, ataxia, hypotonicity, seizures, and mental deterioration develop. The "cherry-red" spot is not seen; there is macular and retinal pigmentation. Death may not occur until the second or third decade.

The neuropathological changes are similar in all three, though in the late forms the changes are less diffuse.[76] The histological picture is characterized by infiltration and ballooning of the ganglion and glial cells from the deposition of a lipid-staining substance identified biochemically as a ganglioside, which is a cerebroside linked to a polyoxyamino acid, neuraminic acid.[73] An increase in the serum neuraminic acid and $\alpha_2$-globulin has been reported.[74,75] Other studies on blood and tissue lipids have revealed normal findings,[76] though vacuolation of the lymphocytes has been described.[77]

*Niemann-Pick Disease.*—This rare congenital familial disorder involving the metabolism of sphingomyelin begins in early infancy and is characterized by progressive mental and physical deterioration, lymphadenopathy, hepatosplenomegaly, and anemia.[71,78] The neurological picture is similar to that seen in infantile amaurotic idiocy, and a "cherry-red" spot in the macula is present in about 60% of patients. Death usually occurs in late infancy. Genetic features include a high rate of consanguineous matings and a recessive pattern of inheritance, with an increased frequency among Jewish infants.

Histologically, there is an accumulation of lipid-filled reticuloendothelial elements (histiocytes) in the liver, spleen, bone marrow, and lymph nodes. The typical Niemann-Pick foam cell is large (50$\mu$ or more in diameter), irregular in size, pale, and vacuolated. The vacuoles contain the lipid-staining material. Demonstration of these typical cells establishes the diagnosis. Lipid deposits are found in the ganglion and glial cells similar to those seen in the familial amauroses.[71] Vacuolation of the mononuclear cells has also been described.[77]

The storage substance has been identified as a diaminophosphatide, sphingomyelin.[79,80]

A glycerophosphatide, lecithin, has also been reported in increased quantities.[80] Disturbances in the serum concentration of these substances have not been found, suggesting that the defect may be an enzymatic disturbance of the intracellular lipid metabolism.

A common pathogenic factor for both the infantile amauroses and Niemann-Pick disease has been suggested by numerous observers on the basis of similar clinical features and histopathological findings.[71] In some families an infantile amaurosis has occurred in one member and Niemann-Pick disease in another. Lipid-staining techniques do not serve to differentiate the diseases.[70] However, the chemical nature of the stored lipids and their distribution in the tissues are dissimilar and suggest that these are separate and distinct diseases; the possibility exists that each is caused by separate but closely related genes.

*Gaucher's Disease.*—Gaucher's disease is a familial disorder of cerebroside metabolism.[71] The onset may occur at any age. There is a chronic form of the disease starting in childhood or adulthood; mental deterioration is usually not present. There is also an acute infantile form where mental deterioration and neurological signs are predominant.[81,82] It begins in the first few months of life with gastrointestinal disturbances, irritability, and enlargement of the liver and spleen. Hypertonicity, seizures, and decerebrate rigidity follow. Death usually occurs in the first year of life. This type of the disease is rare; only some 90 cases in 31 families have been reported in the literature.[71,83]

The reticuloendothelial cells of the liver, spleen, bone marrow, and lymph nodes are filled with a lipid-staining substance. This storage material has been identified as a lipoprotein, the lipid fraction of which consists of a galactose- or glucose-containing cerebroside, kerasin.[84] Although kerasin is present normally in tissues, it is found in excessive amounts in the patient with Gaucher's disease. The typical Gaucher cell is a large (20$\mu$ to 40$\mu$) pale cell with an eccentric nucleus and a wrinkled appearance to the cytoplasm. The finding of this cell in the bone marrow, liver, or spleen is diagnostic of the disease.

Gaucher's disease is a familial illness, though the pattern of inheritance remains uncertain. In addition to the observation of one of us (S. W. W.), there have been a number of instances reported in which one apparently healthy parent has exhibited typical Gaucher cells in the bone marrow. Such a person may transmit the disease to 50% of the offspring in an acute, chronic, or subclinical form, which suggests a dominant pattern of inheritance.[83]

### Disorders of Hormone Synthesis (Cretinism)

"Glandular disturbances" are frequently described among the causes of mental deficiency. Cretinism, or hypothyroidism, however, is the only disorder of hormone function in which mental defect is commonly present. It is doubtful whether other hormonal dysfunction can be etiologically related to mental defect.

There are several types of cretinism. Goitrous, endemic cretinism associated either with insufficient iodine intake or with the ingestion of goitrogenic substances is a well-known entity. It is the result of endemic dietary abnormalities and not of a breakdown in hormone synthesis caused by an enzyme dysfunction. For this reason, no detailed account is given of this type.

There are two distinct groups of cretinism that occur in a sporadic, or nonendemic, manner. They have been found in areas in which dietary iodine intake is sufficient and where goitrogenic compounds are not present. Clinical signs, metabolic abnormalities, and genetic characteristics associated with these two groups are listed in Table 4. The athyreotic, nonendemic cretins comprising the first group are characterized by an absence in embryonic development of the thyroid gland, resulting in an athyreotic state. The patients show little or no

TABLE 4.—*Mental Defects with Disorders of Hormone Synthesis (Nonendemic Cretinism)*

| Disease | Clinical Findings | Metabolic Abnormalities | | Genetics | |
|---|---|---|---|---|---|
| | | Primary | Secondary | Inheritance | Abnormality in Heterozygote |
| Athyreotic nonendemic cretinism | Mental defect, retarded physical and skeletal growth [84] | Congenital absence of thyroid tissue [84] | Decr. $I^{131}$ uptake [84] | Unknown [84, 87] | Unknown [84] |
| Nonendemic familial goitrous cretinism | | | | | |
| Type I | Mental defect, retarded physical and skeletal growth; goiter [88] | Failure to bind inorganic iodine [88] | Incr. $I^{131}$ uptake [88] | Recessive (?) [88] | Unknown |
| Type II | As above [88] | Failure to couple mono- and diiodotyrosine [88] | Incr. $I^{131}$ uptake; incr. thyroidal secretion of iodide; incr. thyroidal mono- and diiodotyrosine; decr. thyroxin [88] | Recessive (?) [88] | Unknown |
| Type III | As above [88, 89] | Absent thyroid deiodinase activity [88, 89] | Incr. serum and urine mono- and diiodotyrosine [88, 89] | Recessive (?) [88] | Partial failure to deiodinate $I^{131}$-labeled diiodotyrosine [88] |

ability to concentrate $I^{131}$, although small amounts of aberrant thyroid tissue may sometimes be demonstrated by $I^{131}$-uptake studies. The onset of the disease is usually in fetal or postnatal life. It depends upon the amount of functioning thyroid tissue and its ability to meet the demands for normal growth.[85] Little is known about the genetics of this disease.[86] Single patients have been described frequently, with but few instances of affected siblings.[87]

Nonendemic familial goitrous cretinism represents the second group.[88-91] Three subtypes have been described, all mainfesting a defect in the synthesis of thyroid hormone. The frequency with which siblings are affected, the increased rate of consanguinity, and the likely enzymatic nature of the defects suggest that these forms of cretinism are inherited in an autosomal recessive pattern.

In the first subtype inorganic iodide is trapped in the thyroid gland but cannot be oxidized to the organic form, i. e., bound to tyrosine.[88] Studies with $I^{131}$ reveal a rapid uptake of radioactive iodide by the gland. The failure to bind iodide is suggested by its prompt release when an iodide-discharging agent, such as potassium thiocyanate, is given. Tissue studies reveal little or no organically bound iodide in the thyroid.

The second subtype is characterized by failure to couple the iodinated tyrosines; mono- and diiodotyrosine are found, but there are only trace amounts of thyroxine. The exact nature of the defect is unknown; a coupling enzyme for the iodinated tyrosyl compounds has not yet been demonstrated.[88]

In the third subtype of goitrous cretinism there is a defect in an iodotyrosine deiodinase which results in a chronic loss of iodide from the body.[88] Thyroid tissue from these patients, in contrast to that of normal persons, shows no ability to deiodinate $I^{131}$-labeled diiodotyrosine; when it is given to these patients, 50% to 60% is excreted intact in the urine, as opposed to a value of 4% in normal persons. The two iodinated tyrosyl derivatives, mono- and diiodotyrosine, can be demonstrated in the blood and are excreted in the urine, thus depleting the body of its iodide stores. The heterozygous state is demonstrated by a partial inability of the gland to deiodinate diiodotyrosine.[88]

In all three subtypes a compensatory hypertrophy of the thyroid occurs, presumably from excess stimulation by thyrotropic hormone. The histopathology reveals follicular hyperplasia, involution, atrophy, and fibrosis, with findings at times similar to those of a fetal adenoma. These three types of metabolic blocks in the synthesis of thyroid hormone suggest that other defects may exist, and evidence for some has already been presented.[88]

The clinical picture in these goitrous cretins is, with few exceptions, rather uniform; dwarfing, mental deficiency, and myxedema are frequent. Signs of hypothyroidism may precede the development of the goiter in some cases. Effective and early treatment may either reduce the size of the goiter or prevent its appearance; in the latter instance an athyreotic state may be suspected. Treatment with thyroxin shows dramatic results, with reversal of most symptoms, except that mental deficiency and impaired growth often remain unaffected.

The effect of replacement therapy with thyroid hormone upon the prevention of mental defect is still a controversial subject. Adequate treatment may be helpful and is always indicated.[90] It has been suggested that a prenatal hormone deficiency may result in cretinism in utero; roentgenologic evidence of this fact has been demonstrated at birth. Generally mental defect is related to the severity and duration of the disease and the time and adequacy of treatment. The prognosis is best when signs of hypothyroidism do not develop until after the age of 3 or 4 years and poorest in infants with athyreotic cretinism.[90]

**Disorders of Possible Metabolic Origin**

There are additional diseases in which mental deficiency is common and in which some metabolic abnormality has been demonstrated. The nature of the metabolic defect is not fully understood, but an enzymatic defect can be suspected, since in some the genetic pattern is well defined. They are difficult to classify into any of the previous groups and are therefore discussed separately. Idiopathic hypercalcemia of infancy, cerebro-ocular-renal disease, nephrogenic diabetes insipidus, maple-sugar urine disease, and congenital familial nonhemolytic jaundice with kernicterus comprise the group. Mongolism is included because increasing evidence points toward the presence of metabolic (enzymatic) abnormalities in this condition. The clinical findings, the metabolic defects, and the known genetic characteristics are listed in Table 5.

In another group of conditions, present knowledge of genetics implies a metabolic origin. Pathology is widespread, often involving multiple organ systems, and mental deficiency is common. As yet, however, no specific metabolic defect has been proved. This category includes several disorders of the connective tissue, e. g., the Ehlers-

TABLE 5.—*Disorders of Possible Metabolic Origin*

| Disease | Clinical Findings | Metabolic Abnormalities | | Genetics | |
|---|---|---|---|---|---|
| | | Primary | Secondary | Inheritance | Abnormality in Heterozygote |
| Idiopathic hypercalcemia of infancy | Mental deficiency, hypotonia, vomiting, hypertension, "elfin" facies [90–98] | Calcium (?) | Hypercalcemia, metastatic calcifications, azotemia, impaired renal function [90–98] | ? | No studies |
| Cerebro-ocular-renal disease | Mental deficiency, glaucoma, cataracts, osteoporosis [100–102] | ? | Metabolic acidosis, aminoaciduria, decr. urinary $NH_3$ [100–102] | ? | Amino-aciduria (?) [101] |
| Nephrogenic diabetes insipidus | Polydipsia, polyuria, dehydration; mental deficiency in some patients [99–101] | ? | Hypotonic urine, vasopressin resistance, hyperelectrolytemia [99–101] | Sex-linked [104, 105, 106, 109] | Polyuria, hypotonic urine in female carriers [106] |
| Maple-sugar urine disease | Neurological and mental deterioration, respiratory difficulties, opisthotonos; urine odor of maple sugar [110, 111] | ? | Increased valine, leucine, isoleucine levels in blood and urine [110, 111] | Recessive (?) [110, 111] | Unknown |
| Congenital familial nonhemolytic jaundice with kernicterus | Mental deficiency, severe neurological signs of kernicterus [113, 112] | Failure to conjugate bilirubin to glucuronide form [112] | Retention of unconjugated bilirubin [113] | Recessive (?) [113] | Unknown [113] |
| Mongolism | Mental deficiency, typical facies and physical characteristics | ? | Incr. serum lipoproteins and urinary β-amino-isobutyric acid; incr. frequency of leukemia and of Alzheimer's disease [114, 115, 117–120] | ? | Incr. frequency of Mongoloid stigmata [121] |

Danlos syndrome and Marfan's syndrome (arachnodactyly) [53]; neurofibromatosis, tuberous sclerosis, and hemangiomatosis (Sturge-Weber syndrome) [123]; the cerebral scleroses and the demyelinating conditions, e. g., Schilder's disease [123] and metachromatic leukoencephalopathy [92]; the chondrodystrophies, e. g., Morquio's disease and achondroplasia [93,123]; the Laurence-Moon-Biedl syndrome,[123] and the ectodermal defects, e. g., Rud's syndrome.[94] These conditions are not discussed in detail here because of the absence of specific metabolic defects. Further research with improved techniques is likely to prove an enzymatic origin in them; in metachromatic leukoencephalopathy the involvement of the kidneys and the presence of a metachromatic substance in the urine sediment have already been demonstrated.[92]

*Idiopathic Hypercalcemia of Infancy.*—A rare disorder of calcium metabolism has recently been described in the literature; 16 cases have been reported. The illness begins in early infancy and is characterized by growth failure, impairment of mental and motor functions, vomiting, a peculiar "elfin" type of facies, hypotonia, purposeless motor activity, and hypertension. Death from infection or renal failure occurs in the first years of life. Osteosclerosis has been noted in all patients; cranial synostosis and nephrocalcinosis, in some.[95-98] The two sexes are affected with equal frequency. It has not been reported in siblings, and a genetic basis for the disease has not yet been described.

Pathological features include metastatic calcification in the kidneys, arteries, myocardium, meninges, and intestinal tract. The kidneys are shrunken and show diffuse calcinosis with interstitial fibrosis and tubular destruction. The parathyroids appear normal. Biochemical findings include an elevated serum calcium and azotemia. The basic defect is unknown. Evidence for increased absorption of calcium from the bowel has been presented, as well as an increased sensitivity to vitamin D.[97] Elevated serum vitamin A levels have also been reported.[99]

A milder form of idiopathic hypercalcemia, without mental deficiency, has been described. This form is self-limited, with improvement occurring during the second year of life. Low calcium and restricted vitamin D intake improved the biochemical status and clinical condition in these infants. Treatment is less successful in the severe form and has no effect on the mental deficiency.

*Cerebro-Ocular-Renal Disease (Lowe's Disease).*—Severe mental deficiency, cataracts, and glaucoma characterize this rare disorder.[100-102] Serum electrolye values reveal a mild uncompensated acidosis. Radiographic changes include osteoporosis and, in a few persons, active rickets. Renal studies reveal an inability to produce ammonia following the infusion of an ammonium chloride solution. Increased values for $\alpha$-amino-nitrogen, amino acids, and other organic acids were found in the urine. Plasma values for glutamine and glutamic acid were increased in one patient.[102] Evidence of glomerular disease was not found. Liver biopsy in one patient produced normal findings.[102] The nature and site of the metabolic defect are not known.

Only a few patients have been described in the literature, and little is known of the genetic pattern. In one instance, both parents were reported to have a generalized amino-aciduria.[101] Combined therapy with vitamin D and a sodium citrate-citric acid mixture will correct the acidosis and, when present, the rickets, but it has no effect on the cataracts or mental deficiency.

*Nephrogenic or Vasopressin (Pitressin)-Resistant Diabetes Insipidus.*—About 20 patients have been described in the literature with this syndrome, manifested by a vasopressin-resistant type of diabetes insipidus, with mental deficiency in some instances. The disease starts in infancy with growth failure, polydipsia, polyuria, and bouts of fever with dehydration.[103-107,109] The ability to concentrate the urine is absent. Hyper-

electrolytemia and nitrogen retention are common, especially during dehydration. Administration of vasopressin has no effect on the concentrating ability of the kidneys. The clinical defect is the inability of the distal renal tubules to respond to antidiuretic hormone. Vasopressin is not inactivated by the patient's serum.[104] Histological studies are few. In one patient microdissection of the kidney tubules revealed "some diminution in proximal tubular convolutions." [107]

The cause of the mental deficiency is unknown, although it is possible that the frequent episodes of dehydration, with associated hyperelectrolytemia, may result in brain damage. It is interesting to note that the mental deficiency seems to occur in certain families [106,109] but has not been reported in other family groups.[104] Several studies suggest that the disorder is sex-linked. In successive generations the disease occurs only in the male, with but one female patient having been described.[105] The carrier state in the female is characterized by a partial inability to concentrate the urine.[108]

*Maple-Sugar Urine Disease.*—Four siblings were recently described with symptoms of progressive cerebral involvement, which started within the first week after birth.[110, 111] The clinical course was characterized by feeding difficulties, absent Moro reflex, irregular respirations, and, later, muscular rigidity and opisthotonos. Death occurred within several weeks, although one patient survived until 20 months of age.[111]

The urine of each infant had an odor similar to that of maple sugar. Attempts to identify the substance responsible for the odor have been unsuccessful. The blood and the urine showed increased levels of valine, leucine, and isoleucine.[111] Changes, possibly secondary, in the concentrations of threonine, alanine, serine, methionine, and cystine were noted. Though an enzymatic defect must be definitely suspected, the site and mechanism are as yet unknown.

*Congenital Familial Nonhemolytic Jaundice with Kernicterus.*— The syndrome is characterized by persistent jaundice and neurological changes of kernicterus beginning in infancy.[112] Mental deficiency is frequent, and life span is short. Death occurs usually prior to one year, and changes of kernicterus can be found in the brain. The serum shows an indirect-reacting bilirubin value of 10 to 44 mg. per 100 cc., and the urinary excretion of injected bilirubin is delayed. The usual causes of jaundice cannot be demonstrated. Microscopically there are bile thrombi in the liver canaliculi. Recent studies indicate that the impaired bilirubin excretion of these patients results from a failure to conjugate bilirubin to form a bilirubin glucuronide.[113] Unconjugated bilirubin is retained in the body, and only trace amounts are found in the urine and bile.

The disorder is rare. It was first studied in three seemingly unrelated families, subsequently found to have a common ancestor. A recessive form of inheritance seems likely. Bilirubin levels and excretion tests on parents were normal.

*Mongolism.*—The symptomatology of this common form of severe mental deficiency is well known, and no purpose would be served by a description of the clinical signs. Discussion will be limited to recent evidence which points to the presence of a biochemical abnormality in this disease.

An increased excretion of $\beta$-aminoisobutyric acid, a reduction product in the catabolism of thymine, has recently been reported.[114] Abnormalities in the $S_f$ 12-20 lipoprotein fraction have been demonstrated by the ultracentrifuge.[115] A significant lowering of the albumin fraction and an increase in the $\gamma$-globulin have been reported, though it is difficult to exclude all exogenous factors in this study.[116] Leukemia has been found with increased frequency in Mongoloid children.[117]

The literature on the pathology of Mongolism leaves much to be desired. Despite the frequency of congenital anomalies of the heart, skeletal system, and intestinal tract, "specific anomalies" of the central nervous system are rare. The brain is described as

showing "nonspecific malformation."[118] Premature aging of the central nervous system has been reported, with plaque formation, neurofibrillary changes, and cell atrophy.[119] This change occurs with greater frequency and at an earlier age in Mongoloid patients than in a control population of other mental defectives.[120]

There is good evidence for a genetic factor in Mongolism, in that no instance of monozygotic twins discordant for Mongolism has been described. Conversely, all twins born discordant for Mongolism have been shown to be dizygotic.[121,122] Mongolism occurs with the same frequency in the co-twin of a dizygotic pair as it does in subsequent siblings.[122] In familial Mongolism a lowered maternal age, as well as an increased frequency of Mongoloid stigmata, occur in the normal mothers and siblings of the patients.[123] Well-documented instances of a Mongoloid mother giving birth to a Mongoloid child or a normal child have been reported.[124,125] It has been suggested that Mongolism may be associated with a common gene, having a frequency of 1 in 5. All homozygotes are susceptible, but, because of maternal protection, only 1 in 27 is affected.[123]

## Comment

There is increasing knowledge concerning the interaction of genes, enzymes, biochemical processes, and behavior, even in such a complex biological unit as a human person.[126] Genes, through their influence upon the production of enzymes, control the biochemical processes in "unit sequences." In accordance with the "one gene-one enzyme" concept, each gene controls the synthesis of a single enzyme or protein. Pauling's theory of "molecular disease" states that abnormal function is often the result of the fabrication of abnormal molecules.[127] Pathology may result from either the absence of an enzyme or its presence in an inactive state.

Unit biochemical processes are easily explainable under this concept. Total human behavior is much more difficult to understand. It is influenced by genetic and "functional" forces. The term "functional" indicates that the concomitant biochemical changes are as yet unidentified. However, where there is activity, mental or other, there is energy consumption, the source of which must be a chemical process. Only on an arbitrary basis can mental functions be separated from chemical changes. The integration of this knowledge is still in an elementary state. A better understanding of the enzymatic mental defects is likely to shed light on mechanisms of genetic actions as well as on the complex processes of normal mental functions.

A convenient disease classification, in accordance with the substrate involved in the metabolic process, is used in this article. A basic biochemical approach would have been more scientific but would have encountered problems of inadequate knowledge. Loss of normal enzyme activity has been conclusively demonstrated only in some conditions, e. g., phenylketonuria (phenlyalanine hydroxylase) and galactosemia (PGal-transferase). The absence of enzyme activity in these conditions leads to the accumulation of their specific substrates, phenylalanine and galactose-1-phosphate.[11-13,36,39-42]

The enzymatic abnormality is not as well understood in the other conditions. In several forms of nonendemic familial goitrous cretinism an accumulation of normal intermediary metabolites of thyroxine synthesis, e. g., iodide, mono-, and diiodotyrosine, has been shown, but an actual loss of enzyme activity has not been demonstrated.[88] Similarly, in H disease the increased excretion of tryptophan, together with its acetic and acetylglutamine derivatives, suggests a specific defect in the metabolism of this amino acid.[21] The pathogenesis of Wilson's disease may be explained as a defect in synthesis of ceruloplasmin or tissue proteins; in either instance the enzyme deficiency has not been demonstrated.[23,25,32] The deposition of a "storage material" in the lipoidoses suggests a block in the intermediary lipid metabolism,[71] and in gargoylism, in the synthesis of

normal connective tissue.[65,66] In congenital familial nonhemolytic jaundice there is evidence for the absence of the enzyme needed to conjugate bilirubin to form glucuronide.[113] In the remaining disorders some manifestations of a metabolic defect have been proven, but neither the nature nor the site of the pathology, nor the enzyme involved, has been determined. The proven biochemical manifestations in them may represent only the secondary effects of an unidentified process, or in some instances they may be the result of an exogenous influence superimposed on a genetic factor.[128]

In those disorders in which a genetic pattern has been established, the evidence strongly suggests that the alteration in metabolism is the direct result of genetic abnormality.[2,126] In some conditions the genetic pattern is recessive, e. g., phenlyketonuria,[6] hepatolenticular degeneration,[23] the infantile amauroses,[71] Niemann-Pick disease,[71] and one type of gargoylism.[56] In another group of disorders, though a recessive pattern of inheritance seems likely, proof is insufficient. These are H disease,[21] galactosemia,[36] familial nonendemic goitrous cretinism,[88] idiopathic hypoglycemia,[47] and congenital familial nonhemolytic jaundice.[112] A sex-linked pattern of inheritance affecting only males is described in vasopression-resistant diabetes insipidus[104,106,109] and in the other type of gargoylism.[57,58] Only in Gaucher's disease has a dominant pattern of inheritance been suggested.[71,83] In the remaining conditions, though a genetic factor is likely, its role remains to be clarified. Cerebro-ocular-renal disease, sucrosuria, idiopathic hypercalcemia, maple-sugar urine disease, and Mongolism fall into this group. In all but Mongolism the rareness of these diseases precludes genetic analysis.

The demonstration of a smaller biochemical defect in the heterozygote further defines genetic control and identifies the carrier state. In phenylketonuria a decreased tolerance to the ingestion of phenylalanine has been shown in the heterozygote.[7] The evidence is less clear in galactosemia, where one or both parents may show a decreased tolerance to galactose; the test, however, lacks reliability.[36,40] In Gaucher's disease typical Gaucher cells are frequently found in the bone marrow of one parent.[71,83] Insufficient information is available to characterize the heterozygous state in idiopathic hypoglycemia,[47] familial nonendemic goitrous cretinism,[88] and cerebro-ocular-renal disease.[101] Even less is known about the heterozygote in the remainder of the disorders.

The frequent coexistence of specific metabolic abnormalities with mental defects implies that the two are etiologically related. Though little is known of the mechanism by which brain function is impaired, it seems unnecessary to invoke the action of a second gene to explain the mental defect.[20] In phenylketonuria the total displacement of chemical homeostasis brought about by an accumulation of metabolites offers a likely explanation for the production of mental deficiency.[20] In hepatolenticular degeneration copper deposited in the tissues may well be the toxic agent producing the neurological and mental impairment.[23-25,32] Excessive quantities of galactose-1-phosphate may have an inhibitory effect on normal cellular metabolism in galactosemic patients.[36,44] The low blood sugar, impairing brain nutrition, may cause the damage in idiopathic hypoglycemia, though other disorders of infancy with similar low glucose levels do not result in mental defect.[45] The infiltration of neurons by storage substances could explain the pathogenesis of mental defect in the lipoidoses and gargoylism.[71] The mental defect might be produced by the lack of thyroxine in cretinism,[88] by repeated episodes of dehydration in vasopressin-resistant diabetes insipidus[106] and idiopathic hypercalcemia,[95] and by the deposition of bilirubin in familial nonhemolytic jaundice.[112] A biochemical explanation is lacking for the pathogenesis of mental deficiency in Mongolism, cerebro-ocular-renal disease, H

disease, maple-sugar urine disease, and sucrosuria.

In enzymatic mental deficiencies the genetic defect is present from conception; yet the time of clinical onset varies. During intrauterine life maternal enzymes protect the fetus from the accumulation of those compounds which are injurious in postnatal life. The infant destined to be a phenylketonuric or galactosemic person, though lacking the necessary enzymes, develops normally in utero. The biochemical changes only appear after birth, precipitated by the ingestion of phenylalanine or lactose. In the galactosemic infant clinical signs appear within a few weeks after birth. In the phenylketonuric patient, though the biochemical changes become evident early, the clinical signs of mental deficiency may not be noted for several months. The unfavorable chemical environment interferes with postpartum development of the brain in the phenylketonuric infant and an arrest in differentiation occurs. The resemblance of the patient's brain to that of the newborn infant supports this hypothesis.

In some conditions clinical onset occurs later in life. In hepatolenticular degeneration, the gradual accumulation of copper produces clinical symptoms only after it has reached a critical level. In H disease symptoms are precipitated by increased demands for nicotinamide or by the accumulation of an unknown metabolite. The clinical onset in the lipoidoses and in gargoylism may depend upon a sufficient accumulation of the storage substance. Knowledge is lacking for an explanation in the other conditions.

Rational treatments are available for phenylketonuria and galactosemia. The results depend upon the time of initiation; therefore, early diagnosis is essential. In H disease the administration of nicotinamide may be beneficial. Steroid therapy is effective in certain forms of idiopathic hypoglycemia. Sodium citrate-citric acid will correct the acidosis in cerebro-ocular-renal disease and idiopathic hypercalcemia, but it has no effect on the mental deficiency. Continuous hydration is important in vasopressin-resistant diabetes insipidus, and the administration of thyroid hormone is beneficial in cretinism. In the remaining disorders no effective form of treatment is known.

Further research into the enzymatic mental defects will add to our understanding of the relationship between mental illness and mental defect.[129,130] Several clinical and biochemical observations suggest a possible common background. Persons with phenylketonuria often present rather bizarre behavior patterns, different from those of other defective children,[4] e. g., an impaired awareness of their surroundings, not proportionate to their degree of mental defect; a failure to respond to strong stimuli, with complete inaccessibility; severe fright reactions; and digital mannerisms which are either slow, methodical, and stereotyped or are rapid and purposeless. Less frequent symptoms include echolalia, perseveration, echopraxia, and catatonic posturing. Their behavior strongly resembles that of a schizophrenic patient.[4]

Increased amounts of indoleacetic and indolelactic acids have been reported in the urine of phenylketonuric patients, suggesting possible derangements in the metabolism of tryptophan and the 5-hydroxyindole compounds.[131] The psychotic behavior of these patients calls attention to the alleged role of these latter compounds, e. g., serotonin (5-hydroxytryptamine), in neurophysiological processes. An increased excretion of diazo-coupling compounds, presumably indoles, has been reported in the urine of schizophrenic persons.[132,133] Lowered serum epinephrine levels have been reported in mentally defective persons.[134]

Anomalies of tryptophan metabolism are often linked to certain types of mental illness; therefore it might be expected that patients with H disease, a disorder of tryptophan metabolism, would present such symptoms. These patients do excrete excess amounts of tryptophan and other indole derivatives in the urine[21] and have been

diagnosed as having pellagra, a condition in which psychotic manifestations are also common. Actually one report has been published of "A Case of Childhood Psychosis with Pellagra," and the patient was subsequently found to have H disease.[22]

Only a small percentage of all mental defectives suffer from conditions discussed in this paper. We have, however, extensive biochemical information about these diseases. Further study will undoubtedly lead us to a clearer knowledge of the biochemical changes which characterize brain function. We may learn of the chemical equilibrium needed for the human to manifest normal intellect and behavior and may acquire the knowledge necessary for a unified understanding of the two syndromes known separately as mental deficiency and mental illness.

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# Abstracts from Current Literature

## American Heart Journal, St. Louis

**Abstracted by Edward C. Matthews, M.D.**

54, No. 5 (Nov.) 1957


* Indications and Contraindications for Open Cardiac Surgery. Henry A. Zimmerman, Earle B. Kay, John MacKrell, and M. P. Sambhi.—p. 727.

On Methods and Complications in Catheterization of Heart and Large Vessels, With and Without Contrast Injection. Marianne Bagger, G. Biörck, V. O. Björk, B. Brodén, L. E. Carlgren, A. Carlsten, I. Edler, B. Ejrup, H. Eliasch, A. Gustafson, A. Gyllenswärd, H. E. Hanson, A. Holmgren, H. Idbohrn, S. R. Johnsson, B. Jonsson, G. Jönsson, J. Karnell, S. R. Kjellberg, H. Krook, H. Larsson, L. Lindén, E. Linder, H. Linderholm, H. Lodin, G. Malmström, E. Mannheimer, T. Möller, J. Philipsson, S. Radner, U. Rudhe, G. Ström, B. Söderholm, F. Ulfsparre, and L. Werkö.—p. 766.

Electrocardiographic Changes Resembling Myocardial Infarction in a Young Child. James E. Doherty and Katherine Dodd.—p. 782.

Ventricular Septal Defect with Aortic Incompetence Simulating Patent Ductus Arteriosus. J. Gordon Claypool, W. Ruth, and T. K. Lin.—p. 788.

Congenital Absence of the Hepatic Portion of the Inferior Vena Cava. Robert F. Grover, Raymond R. Lanier, James K. Lowry, and S. Gilbert Blount Jr.—p. 794.


**Indications and Contraindications for Open Cardiac Surgery.**—The authors discuss their present indications and contraindications for open cardiac surgery with the realization that the criteria are likely to change as clinical experience accumulates.

The presence of an isolated ventricular septal defect, demonstrated by cardiac catherization, is not, in itself, an indication for surgery. In these patients, if the electrocardiogram is normal, if there is no cardiac enlargement, and if the pressure in the right ventricle is within the range of normal surgery may be deferred and the patient may be reevaluated at intervals of two to three years.

Patients with isolated ventricular septal defects who have associated clinical signs and electrocardiographic and roentgen abnormalities become candidates for surgical consideration. Evaluation of pressure determinations, shunt flow estimations, and pulmonary vascular changes permits one to predict which of these patients will tolerate surgical closure of the defect. Patients with high pulmonary artery systolic pressures in the range of 80 mm. Hg and higher are relatively poor surgical risks, but even more important is the relation of the pulmonary artery pressure to the systemic arterial pressure. In the series presented, the authors point out that, in those patients who survived, the pulmonary artery systolic pressure did not exceed 75% to 80% of the systemic pressure. A high pulmonary artery diastolic pressure, indicative of high pulmonary resistance is taken as a poor prognostic sign. The presence of a large right-to-left intracardiac shunt indicates that the patient is not a good surgical candidate. While dye-dilution curves are probably the most satisfactory method of calculating shunt-flow relations in children, the authors feel that the electrocardiogram is often of diagnostic value. In the presence of a dominant left-to-right shunt, the left ventricle shows the diastolic overloading pattern. As pulmonary resistence rises and the left-to-right shunt diminishes, a systolic overload pattern of the right ventricle develops and flattening of the T waves in the left-sided leads appears. The development of advanced pulmonary vascular changes, with medial hypertrophy and intimal thickening of the small muscular arteries, militates against a good result from surgery. Clinical estimation of pulmonary vascular changes is difficult. A drop of 20% in the pulmonary artery diastolic pressure in response to inhalation of 100% oxygen or the injection of aminophylline into the catheter suggests that pulmonary vascular resistance is not fixed at a high level, and, accordingly, the advanced vascular changes of pulmonary hypertension would not be expected. A more precise evaluation of the pulmonary vascular tree may be gotten by obtaining a frozen section of a lung biopsy specimen at surgery before the cardiotomy is started.

The most satisfactory circumstances for closure of a ventricular septal defect exist when the pulmonary artery pressure is below 75% of the systemic pressure, when there is a dominant left-to-right shunt as manifested by a diastolic overloading pattern of the left ventricle in the electrocardiogram, and when a significant drop in pulmonary artery diastolic pressure follows inhalation of 100% oxygen or injection of aminophylline.

The authors recommend that all isolated interatrial septal defects be repaired except in those patients in whom there is reversal of the shunt and in those who are asymptomatic and without roentgen or electrocardiographic abnormalities.

Surgical treatment of isolated valvular pulmonic stenosis is recommended in all patients in whom a definitive diagnosis has been made and in whom there is a gradient across the pulmonary valve at 20 mm. or more of Hg. However, in infants with this lesion who are asymptomatic, it is wise to wait until the age of 4 to 6 years, when the child becomes a better technical risk.

For combined lesions, it is felt that insufficient experience has been accumulated to define specific indications for surgery clearly.

## American Journal of Orthopsychiatry, New York

**Abstracted by Kurt Glaser, M.D.**

### 27, No. 2 (April) 1957


* Orthopsychiatry and Prevention: Symposium, 1956. Exie E. Welsch, Chairman; Lawson G. Lowrey; George S. Stevenson; Abram Kardiner; Ernest M. Gruenberg; Howard Lane, and Julius B. Richmond.—p. 223.

* School Phobia: Workshop, 1955. Alma A. Paulsen, Chairman
  (1) Panic in School Phobia. Mira Talbot.—p. 286.
  (2) School Phobia: Neurotic Crisis or Way of Life. John C. Coolidge, Pauline B. Hahn, and Alice L. Peck.—p. 296.
  (3) Discussion. Adelaide M. Johnson.—p. 307.

The Collaboration of Child Psychiatry, Casework, and Group Work in Dealing with the Mechanism of Acting Out. Marion Barnes, Edward Schiff, and Constance Albee. Discussant: George E. Gardner.—p. 377.


### 27, No. 4 (Oct.) 1957


* The Fathers of Autistic Children. Leon Eisenberg.—p. 715.

* The Development, Meaning and Management of School Phobia: Workshop, 1956. Samuel Waldfogel, John C. Coolidge, and Pauline B. Hahn, Discussant: Hyman S. Lippman.—p. 754.

Fantasies in Children Prior to Herniorrhaphy. Eugene I. Falstein, Ilse Judas, and Robert S. Mendelsohn.—p. 800.

Preliminary Report of a Preschool Therapy Group in a Children's Hospital. Henry H. Fineberg and Margaret Johnson.—p. 808.

A Survey Assessment of Current Parental Attitudes and Practices in Child Rearing. Nyla J. Cole, Orla M. Shaw, Jack Steneck, and Leonard H. Taboroff.—p. 815.

Report of a Constipated Child with Fecal Withholding. Aliza Segall.—p. 823.


**Orthopsychiatry and Prevention: Symposium, 1956.**—In the first part of this article L. G. Lowrey describes the historical development of orthopsychiatry and the American Orthopsychiatric Association, with its original objectives directed essentially toward prevention; the author deplores, however, that in practice most workers in this field are more concerned with the treatment of the sick than with a "preventive, educational job in the community."

The second part, by G. S. Stevenson, outlines possibilities and limitations of preventive mental health measures, tying lack of progress in this area closely to political immaturity, professional rigidity, mass production methods in schools, lack of scientific data in this line, isolation of agencies in this field by their location "off in the county" and/or by voluntary formation of a "hard shell" around them, and, finally, by the inadequate supply of funds under the disguise of poverty. A critical evaluation by A. Kardiner of the cultural factors and their application to prophylaxis is followed by E. M. Gruenberg's epidemiological evaluation of influences of the physical environment, biological factors, and social aspects upon mental health, pointing ways toward a systematic approach to prophylaxis in these areas. H. Lane takes a very critical stand toward present educational methods and facilities, and J. B. Richmond brings public health, medicine, and pediatrics into perspective with mental health, pointing out the need for adequate food, housing, clothing, and school and medical facilities for large parts of the population as a basis for a sound preventive program.

**School Phobia: Workshop, 1955.**—(1) *Panic in School Phobia.*—Twenty-four cases, 16 girls and 8 boys, aged 5 through 15, of average to superior intelligence, suffering from anxiety neurosis—school phobia—are discussed. An overly close relationship of all members of the family, especially between mother and child; great dependency of the mother and father of the child upon their own mothers; immature marital adjustment, and preoccupation with death were noted among the patients studied. Treatment by social case workers involving child, parents, and school personnel is described. The earlier treatment is started the better the results; treatment lasted from two months to two years. Correct timing of the return to school is important, as both delay and too early return may be harmful.

(2) *School Phobia: Neurotic Crisis or Way of Life.*—Of the 27 cases studied, 18 belonged to the "neurotic group," with acute, dramatic onset and clinging behavior but with a generally intact personality. Nine showed deep character disturbances existing from early age.

(3) *Discussion.*—The author points out that the term separation anxiety would be more fitting for this condition than school phobia. Usually a precipitating event, which has to be considered in treatment, precedes the acute onset. She places more emphasis on facing the issue of returning the child to school than on accurate timing and delaying. The discussant does not believe that the dichotomy of neurotic and character-disturbed cases is indicated, believing that the latter are just severer and more insidious cases of the same anxiety, based on difficulties in the mother-child relationship.

**The Fathers of Autistic Children.**—After a review of the symptoms and criteria for diagnosis, based on a study of 100 cases, the author exemplifies the characteristics of fathers of autistic children by presenting three case histories. Eighty-five of the one hundred fathers fell into the category of "obsessive, detached and humorless individuals"; they are well educated, perfectionistic, and preoccupied with minute details and portray a remarkable capacity for concentration. They try to raise "perfect" children who obey, perform, and make no demands.

The personality of the father influences not only the child directly but also the emotional structure of the mother and of the rest of the family. While these characteristics must have some influence upon the development of the child, the author points out that these families also rear normal children, implying the existence of other factors, perhaps within the child, which are necessary to produce childhood schizophrenia.

**The Development, Meaning and Management of School Phobia: Workshop, 1956.**—The authors found that in the 28 boys and 25 girls studied the anxiety invariably originated in a fear of being separated from the mother and was shifted from its basic source to the school. The mother is strongly attached to the child, not necessarily overpermissive but usually overprotective. She feels uncertain about her competence as a mother. The father is usually overconcerned with the child and lowers the mother's self-confidence further by his own attempt to handle the child better than his wife does.

In treating the mother a balance has to be established between support and guidance during the early phase, when she may be very tense, and psychotherapy must be directed toward helping her to assume a more independent and competent role as mother. Treatment of the child was initiated as early as possible, and an attempt was made to return the child to school quickly. "In many of the children the symptom abates as a result of the therapeutic relationship and the opportunity it offers for discharge and clarification." The unconscious conflicts may resolve spontaneously. Very close cooperation with the school was found helpful in this group, and plans were suggested to treat the milder cases within the framework of the school and to refer only the severer cases to the clinic.

The paper is discussed in detail by H. S. Lippman.

## American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

**Abstracted by D. H. Altman, M.D.**

77, No. 2 (Feb.) 1957

* Cardiac Ventriculography. J. Staufter Lehman, Benjamin G. Musser, and Harry D. Lykens.—p. 207.
* The Value of Fast Angiocardiography in the Early Diagnosis of Patent Ductus Arteriosus. J. Lind, M. Rocha, and C. Wegelius.—p. 235.
Percutaneous Splenoportal Venography: Utilizing Rapid Serial Roentgenography. John A Evans and Ward O'Sullivan.—p. 312.

Roentgenologic Findings in Splenic Portography. Andre J. Bruwer and George A. Hallenbeck.—p. 324.
Hemangioma of the Liver Diagnosed by Splenoportography. Samuel Levine.—p. 332.

## 77, No. 5 (May) 1957

* Radiation Therapy in the Treatment of Retinoblastoma. Ivor G. Williams.—p. 786.

## 77, No. 6 (June) 1957

* The Familiar Occurrence of Pulmonary Alveolar Microlithiasis. Merrill C. Sosman, Gerald D. Dodd, W. Duane Jones, and George U. Pillmore.—p. 947.

**Cardiac Ventriculography.**—This article is of primary interest to those persons who are dealing with the diagnosis of cardiac lesions by some of the newer methods, including angiography and cardiac catherization. Although the article does not actually discuss any cases in the pediatric age group, 77 cases are reviewed. These 77 cases include one patient 16 years and one 18 years of age, and the other patients, are in the third to seventh decades of life. The use of direct cardiac injection of opaque medium into the ventricle was first reported by Navoli, in 1936, and the first report of any significant number of cases was by Ponsdonenech and Nunez, in 1951, who reported 30 cases. The authors' series began in 1956, and their experience in 77 cases is reported. The method and material to be used in this procedure are described in some detail, and the study seems to show considerable value in determining the degree of mitral insufficiency. The method also seems to hold promise in evaluating the aortic value and possibly for evaluating interventricular septal defects. The article is recommended for those who are interested in this newer method of direct chamber study.

**The Value of Fast Angiography in Early Diagnosis of Patent Ductus Arteriosus.**—The difficulty of diagnosing patent ductus arteriosus in infants and in young children is well known. The typical machinery murmur is not present until the diastolic pressure of the systemic circulation is higher than that of pulmonary circulation. Certain criteria are established as important in the indirect diagnosis of patent ductus arteriosus in this early age group and are as follows: (1) aortic infundibular dilatation; (2) pulmonary artery dilatation; (3) elevation of the truncus-conus pulmonary artery and its left main branch; (4) increased pulmonary artery output; (5) dilution of contrast medium in the pulmonary artery best seen in ventricular systole; (6) prolonged circulation of contrast medium in the pulmonary vessels; (7) left atrial and left ventricular enlargement; (8) refilling of the pulmonary artery in later phases of angiography.

These indirect signs are of importance in the diagnosis as passage of opaque medium from the aorta into the pulmonary artery is actually not seen except in the occasional case, as the ductus has a hidden position. The use of the biplane angiogram improves chances of demonstration to some extent, but even here the demonstration is not always accomplished. On the one hand, because of the desirability of being able to establish the diagnosis of patent ductus arteriosus at an early age for surgical consideration and, on the other hand, because of the technical difficulties in obtaining satisfactory direct anatomic visualization of the patent ductus arteriosus, every additional aid is necessary when the malformation is suspected, and these signs are best seen by use of the fast angiographic technique. This suggests the use of techniques which will permit serial filming, such as can be done by cineroentgenography.

**Radiation Therapy in the Treatment of Retinoblastoma.**—Retinoblastoma is a rare tumor, occuring 1 time in 34,000 live births. Sixty per cent of cases appear during the first three years of life, and only about five per cent occur after the age of 6 years. The inability of the young child to express visual difficulty is responsible for delay in the diagnosis. There have been reports of this tumor occurring in families. It is also one of the tumors in which spontaneous regression has occurred. The disease is bilateral in approximately 20% of cases. The tumor is usually rapidly growing and highly malignant.

This paper deals primarily with primary tumor in the eye and cases in which the disease has not extended. The Foster-Moore series of five patients treated from 1929 to 1934 with radon seed revealed that four patients were alive and well 22 to 27 years later. One patient died immediately postoperatively. On this basis, Stallard treated 15 cases up until 1948. All of these cases were under 3 years of age, and 14 of them had bilateral tumor. Of the 15 cases treated, 1 died of unknown cause one year after irradiation, and in this patient no

evidence of tumor was seen at autopsy. Of the remaining 14 cases all are alive today. Nine of these patients, or 60%, had sufficient sight for educational purposes. One had an eye excised for suspected recurrence, and four others are blind as a result of retinal detachment or hemorrhage. The specific types of changes associated with the irradiation are reported.

On the basis of this study further progress was felt to depend upon accurate assessment of the physical conditions, and the new applicators to be used were constructed on definite physical principles. The construction of these disks is explained in considerable detail. The present disk utilize $Co^{60}$ instead of a radium salt. The technique for application is also described in detail.

The second Stallard series, in which the cobalt disks were used, was based on 36 patients treated between 1948 and 1955. These were divided into two groups. The first group was a group of 28 patients in whom one-third or less of the retina was involved in the neoplasm. These were treated by radioactive cobalt alone. Of these patients, 28 are apparently cured to date. Of these, 20 have vision, of 3 the vision is unknown, and 5 had the macula destroyed. Six of these patients have survived for five years or longer. A second group of eight patients was treated by deep roentgen rays and then with radioactive cobalt disks to the residue of the neoplasm. In all of these cases more than one-half of the retina was involved in the neoplasm, and so the prognosis was almost hopeless. One has some vision, and three are blind, two as a result of retinal detachment and the other because of a vitreous hemorrhage. Four had had the blind irradiated eye excised.

This paper is recommended to all those who have had the occasion of determining therapy in a patient with retinoblastoma.

**The Familial Occurrence of Pulmonary Alveolar Microlithiasis.**—This article, although dealing primarily with a disease producing symptoms in the adult, is of pediatric significance because of the increasing frequency of its recognition and its familiar occurrence. The article is 65 pages in length, as it summarizes the 21 cases previously reported in the world literature to date and, in addition, gives a relatively complete case history on each of 23 cases personally known of by the authors. Thirteen of these twenty-three new cases occur in five families. The disease has been seen in children, one 8 years of age and one each of 10 and 12 years. Nine patients under 20 years of age are known to have this disorder. The etiological cause is unknown. The majority of cases are discovered accidentally by routine x-ray examination. Its occurrence in families suggests an inherited abnormality or defect in pulmonary metabolism. There is a long clinical course to the disease, and pulmonary insufficiency occurs years after recognition of the lesion roentgenologically. The most frequent symptoms are those of pulmonary insufficiency and shortness of breath on exertion. The disease is manifested radiographically by a fine sand-like spread of particles uniformly throughout both lung fields. These particles are of calcific density, with only slight variation in size, sometimes accentuated along the pleural surfaces, but not conglomerate or colescent. There are millions of these small densities, and the total density produced by the tiny particles is frequently sufficient to obscure outlines of the heart and diaphragm. The differential diagnosis is between miliary tuberculosis; pulmonary infections, particularly of the fungi, and pneumoconiosis, such as beryllosis, silicosis, asbestosis, and bagassosis. The pneumoconiosis occurs primarily in the upper lobe, whereas this disorder occurs primarily in the lower lobes, and also in this disorder there are discrete shadows of calcific density not seen in other disorders. Lesions due to industrial hazards of welding and working with tin (stannosis) resulting from tin oxide inhalation and barium inhalation can give a somewhat similar radiographic picture.

Sarcoidosis is a disorder which can produce extensive changes in the lung fields similar to those of pulmonary alveolar microlithiasis and is also a disorder in which there are a minimal number of symptomatic findings. Miliary metastases to the lungs and lymphangitic carcinomatosis are other disorders to be considered.

In the child the occurrence of pulmonary hemosiderosis is a disorder which can produce radiographic findings very similar to those of pulmonary alveolar microlithiasis.

The article is a classic article in describing in minute detail the complete picture of this heretofore seldom reported disorder.

## Annals of Internal Medicine, Lancaster, Pa.

**Abstracted by Brian Kiely, M.D.**

### 46, No. 1 (Jan.) 1957

Problems in the Management of Ulcerative Colitis, with Particular Reference to ACTH and the Adrenal Steroids. Manuel Sklar, Joseph B. Kirsner, and Walter L. Palmer.—p. 1.

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° Polycythemia of Obesity: Further Studies of Its Mechanism and a Report of Two Additional Cases. Max H. Weil and Ananda S. Prasad.—p. 60.

Amino-Aciduria with Cystinosis: Case Report with Determination of Urinary Amino Acids and Ocular Cystine. Philip L. Dern.—p. 138.

Goiters in Twins Resulting from Propylthiouracil Given During Pregnancy. Le Roy K. Branch and Sanford W. Tuthill.—p. 145.

### 46, No. 2 (Feb.) 1957

Pituitary Tumors. Carl W. Rand and Herbert W. Rand.—p. 301.

Corticotropin and Adrenal Steroids as Adjuncts to the Treatment of Tuberculous Meningitis. J. Richard Johnson, Nancy E. Furstenberg, Roy Patterson, Henry K. Schoch, and Winthrop N. Davey.—p. 316.

Use and Abuse of Anticholinergic Drugs in the Management of Gastrointestinal Disease. Alvin J. Cummins.—p. 352.

Postural Adjustments and Protein Excretion by the Kidney in Renal Disease. S. Edward King.—p. 360.

° Serotonin (Editorial). F. J. Borges and S. P. Bessman.—p. 425.

### 47, No. 5 (Nov.) 1957

° Our Growing Understanding of Thyroid Function and Its Clinical Application. J. Howard Means.—p. 853.

Long Term Follow-Up of Patients with Healed Bacterial Endocarditis. Buford Hall.—p. 880.

A Few Notions Involved in the Clinical Use of Radioisotopes. Gould A. Andrews.—p. 922.

Evidences for Clinical Magnesium Deficiency. Edmund B. Flink, Robert McCollister, Ananda S. Prasad, James C. Melby, and Richard P. Doe.—p. 956.

Chelation (Editorial). Samuel P. Bessman and Norman J. Doorenbos.—p. 1036.

**Polycythemia of Obesity: Further Studies of Its Mechanism and a Report of Two Additional Cases.**—In recent years an association of polycythemia with obesity has been observed at three medical centers, and physiologic studies have been made by the present authors in four cases which demonstrate a specific syndrome. The patients are extremely obese. The hematologic findings are confined to the red cell series and consist of elevation of the hemoglobin, hematocrit, and red cell count; increased red cell volume with decreased plasma volume; possibly increased mean corpuscular volume, and erythroid hyperplasia in the bone marrow. Unlike in the situation polycythemia vera, the myeloid series and platelets are not affected. Respiratory abnormalities include shallow breathing; dyspnea, at first on exertion and later at rest; Cheyne-Stokes respiration; cyanosis; decreased vital capacity; little or no change in the chest circumference between maximal inspiration and expiration; elevated carbon-dioxide-combining power of the blood, and low arterial oxygen saturation which is aggravated by exercise, improved by hyperventilation, and corrected by breathing 100% oxygen. Congestive heart failure is a common complication. The patients tend to be somnolent.

Since the whole syndrome can be reversed by weight reduction alone, it is probable that the initial abnormality is mechanical interference with alveolar ventilation due to the presence of fat in and around the thoracic cavity; arterial desaturation, carbon dioxide retention, polycythemia and all the attendant symptoms result.

**Serotonin.**—Serotonin (5-hydroxytryptamine) is a hormone produced by various tissues and having diverse physiologic actions. It has been found in clotted blood or blood mechanically traumatized by perfusion pumps, where it has been released by platelets; in the venom of the toad; in the cromaffin cells of the intestine; in carcinoid tumors; in brain tissue, and in the plasma in anaphylactic shock. The synthesis of serotonin begins with tryptophane, which is hydroxylated, probably in the liver only, to form 5-hydroxytryptophane. Decarboxylation of the latter in the liver, intestine, kidney, and brain produces the active substance, 5-hydroxytryptamine. Most tissues, but especially the liver and lungs, contain amine oxidase by which serotonin is inactivited by conversion to 5-hydroxyindoleacetic acid, which is excreted in the urine and is a useful index of serotonin activity.

Several drugs affect the metabolism of serotonin. Reserpine causes it to be discharged from the brain, intestines, and platelets and excreted as 5-hydroxyindoleacetic acid. Marsalid

inhibits amine oxidase and slows the destruction of serotonin. Chlorpromazine blocks its action on the isolated intestine.

When injected, the hormone affects the cardiovascular and gastrointestinal systems, producing tachycardia, vasodilatation and cyanosis of the skin, colic, borborygmus, and diarrhea. These same symptoms occur intermittently in patients with carcinoid tumors, who also acquire pulmonary stenosis and endocardial fibrosis in the right side of the heart and excrete excessive amounts of 5-hydroxyindoleacetic acid. Although analogues of 5-hydroxytryptamine, including lysergic acid, have a profound effect on the central nervous system, injection of the compound itself does not. In perfusion experiments, serotonin released by platelets causes vasoconstriction unless intact lungs or liver are included in the system. Other areas in which serotonin is suspected of having a role are the production of pulmonary embolism, bronchial constriction, and antidiuresis.

**Our Growing Understanding of Thyroid Function and Its Clinical Application.**—The synthesis of thyroid hormone begins with the uptake of iodide from the blood stream by thyroid cells by an unknown mechanism. Iodide is oxidized to iodine, then attached to tyrosine to form diiodotyrosine, two molecules of which are coupled with the loss of a side-chain to form tetraiodothyronine, or thyroxine. Monoiodotyrosine, diiodothyronine, and triiodothyronine are also synthesized and may have some functional importance; triiodothyronine possesses all the physiologic actions of thyroxine, and the relative natural importance of those two compounds is known. Thyroid cells also produce the protein thyroglobulin, to which the iodinated molecules are attached and deposited in the follicles in the form of colloid. Hormone is released from the gland by a proteolytic enzyme which breaks down the colloid so that the smaller molecules may enter the blood stream, where they are carried in loose combination with plasma proteins. Very little is known about the mode of action of the hormone molecules on the target cells or of their catabolism. Current investigations of this question are focusing attention on the mitochondria, which seems to be the centers of energy transformations in the cell.

The underlying abnormality in Graves' disease is unknown. In endemic colloid goiter there is simply insufficient intake of iodine; the thyroid cells continue to produce thyroglobulin which accumulates in excessive amounts without the iodinated molecules. In "Iodbasedow" (hyperthyroidism due to iodine administration) the accumulated protein is suddenly supplied with the iodinated moiety and large amounts of effective hormone are formed and released. In sporadic colloid goiter (colloid goiter occurring in the absence of dietary deficiency of iodine) a variety of metabolic defects have been discovered in various cases. The oxidation of iodide to iodine, the coupling of tyrosine to form thyronines, or a block in the deiodination of diiodotyrosine causing loss of iodine in the urine have each been demonstrated; all result in deficiency of hormone, compensatory goiter, and finally clinical hypothyroidism.

## Archives of Disease in Childhood, London

**Abstracted by R. Janet Watson, M.D.**

32, No. 165 (Oct.) 1957

Veno-Occlusive Disease of the Liver and Indian Childhood Cirrhosis. D. B. Jelliffe, F. Bras, and K. L. Mukherjee.—p. 369.
Deciduous Tooth Eruption. Frank Falkner.—p. 368.
Blood Oxygen Studies in Premature Infants. P. M. Russell and F. P. Hudson.—p. 392.
Low Oxygen Tension in the Management of Newborn Infants. S. Sjöstedt and Gösta Rooth.—p. 397.
Amino-Aciduria and Hypermetabolism in Progeria. A. H. Steinberg, A. Szeinberg, and B. E. Cohen.—p. 401.
The Applications of Serum Lipoprotein Electrophoresis in Paediatric Practice. H. B. Salt and O. H. Wolff.—p. 404.
The Urinary Phenolsulphonphthalein (Phenol Red) Excretion Test in Hydrocephalus. K. M. Laurence.—p. 413.
Reducing Sugars in the Urine and Blood of Premature Babies. J. C. Haworth and M. S. MacDonald.—p. 417.
Congenital Idiopathic Hypogammaglobulinaemia. K. M. Pearce and M. S. Perinpanayagam.—p. 422.
Chronic Neutropenia. Muriel M. McLean.—p. 431.
° Wheat Gluten and Coeliac Disease. C. Alvey, C. M. Anderson, and M. Freeman.—p. 434.
Palpability of the Liver and Spleen in Infants and Children. Brian McNicholl.—p. 438.
B. C. G. Tuberculin. John Lorber.—p. 441.
The Hypersensitivity Reactions to Para-Aminosalicylic Acid (P. A. S.). Stuart Carne.—p. 446.
The Diagnosis of Pertussis with Supralaryngeal and Modified Pernasal Swabs. Andrew Bogdan.—p. 450.
The Significance of the C-Reactive Protein Estimation in Streptococcal and Allied Disease. S. F. Dawson.—p. 454.

Cerebral Abscess as a Complication of Neonatal Sepsis. N. R. Butler, H. Barrie, and K. W. E. Paine.—p. 461.
Hydatid Cyst of the Kidney in a Child. M. E. Broughton.—p. 466.
* Radial Nerve Palsies in the Newborn. Geoffrey V. Feldman.—p. 469.

**Wheat Gluten and Coeliac Disease.**—The authors investigated 28 of their patients with celiac disease in regard to the mechanism of the harmful effect of wheat gluten. No evidence of an allergic effect could be found. Digestion of gluten to the peptide stage appeared to be normal in these children. Neither glutamine nor an amino acid digest of gluten fed to these patients had any harmful effect; however, various intermediate fractions, such as a tryptic digest and a water-soluble dialysate of this, produced a recurrence of steatorrhea. An abnormally high increase in blood glutamine was observed to follow a dose of gluten or gliadin. The authors concluded that the toxic effect of gluten is due to a peptide containing glutamine and that there may be a deficiency of a specific intracellular enzyme necessary for the deamination of this peptide.

**Radial Nerve Palsies in the Newborn.**—The author describes eight newborn infants with radial nerve palsy manifested by wrist drop with recovery in one week to three months. In two cases there was bilateral involvement. Two patients had areas of fat necrosis at sites overlying the course of the radial nerve. Labor was unduly prolonged in six instances, and the author postulated that a uterine constriction ring might have been the causative factor for the radial nerve injury.

## Blood, New York

**Abstracted by Audrey K. Brown, M.D.**

### 12, No. 8 (Aug.) 1957

Variation in the Duration of Survival of Patients with Acute Leukemia. Brian MacMahon and Donald Forman.—p. 683.
* Studies in Leukemia: VII. The Induction of Leukemia in Swiss Mice by Means of Cell-Free Filtrates of Leukemic Mouse Brain. Harold M. Schoolman, Wilma Spurrier, Steven O. Schwartz, and Paul B. Szanto.—p. 694.
An Abnormal Hemolytic System Associated with Leukemia and Other Disseminated Malignant Diseases. William H. Crosby and Naomi R. Benjamin.—p. 701.
In Vitro Effects of X-Radiation of White Blood Cells and Blood Platelets. Richard Wagner, Norma Meyerriecks, and Carroll Z. Berman.—p. 733.
Experimental Treatment of Total-Body Irradiation Injury: A Brief Review. C. C. Congdon.—p. 746.
Therapeutic Results in Treatment of Hodgkin's Disease with CB 1348 and R-48. Antonio Rottino.—p. 755.

### 12, No. 9 (Sept.) 1957

A Consideration of Myeloid-Erythroid Balance in Man. Harvey M. Patt.—p. 777.
Leukemia or Lymphoma and Coexistent Primary Malignant Lesions: A Review of the Literature and a Study of 120 Cases. Charles G. Moertel and Albert B. Hagedorn.—p. 788.
* The Role of the Mature Neutrophil in Bacterial Infections in Acute Leukemia. Richard T. Silver, Grace A. Beal, Marvin A. Schneiderman, and Norman B. McCollough.—p. 814.
The Osmotic Resistance of Leukocytes in Peripheral Blood and Splenic Circulation of the Rabbit. E. Storti, L. Bellesia, and E. Lusvarghi.—p. 829.
* The Nature of the Hemorrhagic Disorder Accompanying Hemolytic Transfusion Reactions in Man. Julius Krevans, Dudley P. Jackson, C. Lockard Conley, and Robert C. Hartmann.—p. 834.

**Studies in Leukemia: VII. The Induction of Leukemia in Swiss Mice by Means of Cell-Free Filtrates of Leukemic Mouse Brain.**—Cell-free filtrates prepared from brains of leukemic AKR mice had been demonstrated previously to accelerate development of leukemia in approximately 50% of AKR mice in three to five weeks after a single intracerebral or intraperitoneal injection. Since spontaneous leukemia develops frequently in AKR mice, similar studies were undertaken in a strain of mice in which leukemia is rare.

As a source of agent, filtrates from leukemic tissues orginating in a Swiss mouse were used. This mouse had been caged with AKR males for the purpose of hybrid breeding and had developed a "spontaneous" lymphoblastoma resembling the disease in the AKR strain.

Tumor-cell suspension of this animal did not grow when inoculated into AKR mice but did grow in both Swiss and DBA mice, producing leukemia.

While cell-free filtrates of leukemic tissue failed to produce leukemia, cell-free filtrates of leukemic Swiss or DBA mouse brain induced leukemia in 48 of 106 Swiss mice inoculated intracerebrally and 39 of 55 animals inoculated intraperitoneally. The incidence of spontaneous leukemia in this strain is about 1%.

The findings suggest that the filterable agent is concerned with initiation of a leukemic process rather than with acceleration of a latent potential.

**The Role of the Mature Neutrophil in Bacterial Infections in Acute Leukemia.**—Acute leukemia is frequently complicated by frequent and severe infections. Cellular defense against infection in leukemia has been studied previously, but the findings have been conflicting and the factors relating to susceptibility to infection, as well as the relationship of infection and remission in acute leukemia, are not defined. In this study, observations were made of the relationship of the number of circulating mature neutrophils to the onset of bacterial infection in acute leukemia.

Phagocytosis of Brucella organisms by mature neutrophils was studied in acute leukemia and found to be normal and unaltered by antimetabolite therapy or by the presence of bacterial infection.

The onset of bacterial infection in acute leukemia was preceded by marked decreases in mature neutrophil counts. As infection did not always follow decrease in mature neutrophils, it seems that other factors also influence the development of bacterial infections in patients with acute leukemia.

**The Nature of the Hemorrhagic Disorder Accompanying Hemolytic Transfusion Reactions in Man.**—Hemolytic transfusion reactions have been associated with the development of a hemorrhagic tendency. This study concerns two patients who developed abnormal bleeding after inadvertent administration of 500 cc. of incompatible blood. Hypofibrinogenemia, hypoprothrombinemia, and thrombocytopenia were observed in both.

Evidence is presented supporting the concept of intravascular clotting, which could be brought about by a thromboplastin-like activity of lysed red blood cells, as the most likely etiology of this disorder.

The authors emphasize that hemorrhage may be the first sign of a hemolytic transfusion reaction. Administration of fresh whole compatible blood with supplementary fibrinogen would be indicated.

## Circulation, New York

**Abstracted by Anthony C. Nolke**

16, No. 5 (Nov.) 1957

The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life: I. Prognosis with Special Reference to Survivorship. May G. Wilson and Wan Ngo Lim.—p. 700.
The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life: II. Prognosis with Special Reference to Morbidity. Melville G. Magida and Franklin H. Streitfeld.—p. 713.
* Tetralogy of Fallot: Clinical and Hemodynamic Spectrum of Combined Pulmonary Stenosis and Ventricular Septal Defect. Malcolm C. McCord, Jack van Elk, and S. Gilbert Blount Jr.—p. 736.
Quantitative Analysis of the Electrocardiographic Pattern of Hypopotassemia. Borys Surawicz, Harold A. Braun, William B. Crum, Robert L. Kemp, Seymour Wagner, and Samuel Bellet.—p. 750.
Clinical Conference: Symposium on Diagnostic Methods in the Study of Left-to-Right Shunts. Robert P. Grant, Richard J. Sanders, Andrew G. Morrow, and Eugene Braunwald.—p. 791.

**Tetralogy of Fallot: Clinical and Hemodynamic Spectrum of Combined Pulmonary Stenosis and Ventricular Septal Defect.**—The authors describe the original concept of tetralogy of Fallot as a simple entity which is no longer valid. They demonstrate the lesion as occupying a broad spectrum in the field of congenital heart defects and presenting itself in numerous and various forms. They point out that, while the entity has been called a tetralogy, there are only two features (the pulmonary stenosis and the ventricular septal defect) which are essential in determing the clinical and physiologic patterns of this lesion. Right ventricular hypertrophy, which is given as one of the classic components of the tetralogy, is described as purely a secondary effect and is discussed as a significant factor in the determination of the clinical picture. The role of dextroposition of the aortic root was thought to be more difficult to evaluate and not so easily dismissed. However, the authors felt that clinical and physiologic evidence together with findings at surgery suggested that the dextroposition of the aorta is of functional origin and not anatomic.

The authors classified the tetralogy of Fallot on the basis of the possible combinations of infundibular stenosis of varying severity and a ventricular defect of varying size. A spectrum composed of these combinations was presented within the group, which yet permitted definition

of recognizable subdivisions. The first three groups of this spectrum represented three well-known forms of the tetralogy of Fallot, in which two component lesions are of about equal but varying severity. The remaining two subdivisions consisted of forms of the tetralogy in which one lesion is very severe and the other is relatively mild, resulting in the hemodynamic pattern of the dominant defect.

Type I consisted of extreme tetralogy; this group possessed an extreme pulmonary stenosis or complete atresia of the pulmonary artery with a large ventricular septal defect. Type II consisted of the classic tetralogy; this group possessed severe pulmonary stenosis and a large ventricular septal defect. Type III consisted of mild tetralogy; this group was described as possessing mild or moderate degrees of pulmonary stenosis with a small or moderately-sized ventricular septal defect. Type IV consisted of those cases which exhibited a dominance of the ventricular septal defect; this group was defined by the presence of mild infundibular stenosis with a large ventricular septal defect. Type V consisted of those cases exhibiting a dominance of pulmonary stenosis; this group possessed severe right ventricular outflow obstruction and a small ventricular septal defect.

It was felt by the authors that the use of the term tetralogy of Fallot is misleading because of the broad spectrum which this entity really possesses and that the term probably should be discarded for a better understanding of the clinical and physiologic features of the condition.

## Maandschrift voor kindergeneeskunde, Leiden, Netherlands

**Abstracted by S. van Crevald**

### 25:266-299 (Aug.) 1957


* Excretion of Phenylalanine in Two Patients with Oligophrenia Phenylpyruvica. J. H. P. Jonxis.—p. 272.
* Experiences with the Treatment of Tuberculous Meningitis Since the Introduction of INH. C. Hooft and H. van Winckel.—p. 280.
* The Treatment of Blindness in Tuberculous Meningitis. W. van Zeben and H. Verbiest.—p. 294.


### 25:301-335 (Sept.) 1957


* Partition of Lipoproteins in Different Pathologic Conditions. C. Vandenberghen and M. van Belle.—p. 301.
* Septicemia Caused by Diplococcus Crassus. J. Pintelon.—p. 323.


### 25:337-367 (Oct.) 1957


* Problems of Leukemic Children. E. E. Brongers.—p. 337.
* About the "Rooming-In" System in Pediatric Hospitals. R. G. de Benedetti.—p. 342.
* Thrombotic Thrombocytopenic Purpura. J. Engelhardt and H. E. Schornagel.—p. 349.


**Excretion of Phenylalanine in Two Patients with Oligophrenia Phenylpyruvica.**—Two patients with oligophrenia phenylpyruvica are described. On a diet poor in phenylalanine the phenylalanine plasma levels went down to about normal values. During periods when the nitrogen balance was not positive, the plasma levels rose again with the same phenylalanine-poor diet. The phenylalanine clearances of these patients was the same as those of normal children, although the phenylalanine plasma levels were about 10 times too high.

**Experiences with the Treatment of Tuberculous Meningitis Since the Introduction of INH.**—Between July 1, 1952, and June 20, 1956, forty cases of tuberculous meningitis were admitted to the pediatric clinic of the University of Ghent (Belgium). There were 35 cases which remained for detailed analysis; 5 cases died. The dosage of isoniazid (INH) must be more than 10 mg. per kilogram of body weight daily but needs not to be more than 20 mg. per kilogram of body weight daily. The authors claim a duration of treatment of six to eight months to be sufficient.

INH has much improved the prognosis. It has made intrathecal therapy completely impossible. With early diagnosis, a recovery rate of 100% may be obtained.

**The Treatment of Blindness in Tuberculous Meningitis.**—Despite the improvement of the prognosis of tuberculous meningitis in recent years, particularly due to the introduction of isoniazid (INH), blindness is still an occasional complication. The probable cause of this blindness is a local arachnoiditis or tuberculous granulation tissue which presses on the optic nerves.

The case histories of three patients are discussed; in each of these the optic chiasma was explored and a description is given of the findings at operation.

The therapy consists in the removal of adhesions and granulation tissue and the subsequent bringing in of a small plastic drain through which streptomycin and INH can be administered locally for some weeks. The results obtained with this method of treatment are good.

**Partition of Lipoproteins in Different Pathologic Conditions.**—In different diseases the authors studied the variations in protein- and lipidograms.

In chronic glomerulonephritis there was a moderate to strong $\alpha$-lipoprotein decrease and $\beta$-lipoprotein increase.

Viral hepatitis showed $\alpha$-lipoproteins on the lower limit of normal, together with raised $\beta$-lipoprotein values.

The lipidogram in myxedema was characterized by an increase of $\beta$-lipoproteins.

Reticulosis of the Hand-Schüller-Christian type gave normal $\alpha$-lipoproteins, the $\beta$-lipoproteins being very sharply defined, and exactly localized on the $\beta$-globulin site. Chylomicrons in these cases were low.

In dermatomyositis $\alpha$-lipoprotein values were decreased, while the $\beta$-lipoproteins were found increased and localized on the $\beta$-globulin spot.

**Septicemia Caused by Diplococcus Crassus.**—The author observed two cases of septicemia caused by Diplococcus crassus. The first case was a septicemia of chronic course, starting at the age of 3 weeks with acute dacryocystitis and osteomyelitis of the left maxillary bone. At 9 months a large abscess appeared on the midline in the upper dorsal region. Later a meningitis developed with Diplococcus crassus in the spinal fluid. With penicillin and erythromycin treatment combined with dacryocystectomy complete cure was finally obtained.

The second case concerned a 7-year-old girl. Here the disease started with an acute arthritis of the left knee joint. Despite penicillin and erythromycin treatment, the patient died. At autopsy collapse of both lungs with numerous subcortical abscesses was found.

**Problems of Leukemic Children.**—This article is a discussion of the attitude of medical and nursing staff toward leukemic patients and their relatives during treatment.

**About the "Rooming-In" System in Pediatric Hospitals.**—The author, active at the center of mental hygiene of the pediatric clinic of the University of Rome (Prof. Frontali), discusses in this article the problem of "rooming in" in pediatric hospitals not only for the newborn but also for pediatric patients in general.

**Thrombotic Thrombocytopenic Purpura.**—A case of thrombotic thrombocytopenic purpura is described in a girl 1½ years old. Treatment with corticotropin (ACTH) was given, without any noticeable influence on the disease.

## Medical Journal of Australia, Sydney

**Abstracted by George H. Lowrey, M.D.**

### 2, No. 5 (Aug. 3) 1957

Pitfalls in the Treatment of Enuresis by an Electric Awakening Machine; John Bostock and Marjorie Shackleton.—p. 152.

Psychiatric Aspects of Childhood Epilepsy. Edward J. A. Nuffield.—p. 158.

### 2, No. 6 (Aug. 10) 1957

Maternal and Foetal Prognosis in Toxaemias of Pregnancy. F. J. Browne.—p. 198.

### 2, No. 7 (Aug. 17) 1957

* A Biochemical Approach to Calomel-Induced Mercurialism and to the Aetiology of Pink Disease. F. R. Barrett.—p. 242.

Observations on Prophylaxis of Measles with Gamma Globulin. B. Stafford.—p. 248.

The Treatment of Severe Tetanus. Brian Dwyer and L. Lazarus.—p. 249.

### 2, No. 8 (Aug. 24) 1957

Radiological Aspects of Portal Hypertension. H. G. Hiller.—p. 278.

Enuresis and Pants-Wetting in Children: A Survey of Some Simple Therapies. John Bostock and J. P. Eckert.—p. 284.

2, No. 10 (Sept. 7) 1957

Pepsinized Grass Pollen in the Treatment of Hay-Fever: A Further Report. R. S. Colton and H. N. Robson.—p. 353.

* The Use of Chlorpromazine to Control Spasm and Rigidity in Tetanus: Report of a Case. F. I. R. Martin.—p. 360.

2, No. 11 (Sept. 14) 1957

Six Year Follow-Up Mantoux Survey of Aborigines in Western Australia. F. G. B. Edwards, K. W. Harris, and S. E. Slade.—p. 383.

2, No. 12 (Sept. 21) 1957

Epilepsy in Childhood. Eric Davis.—p. 420.

Interictal Events in the Childhood Epilepsies: Their Psychiatric Significance. E. J. A. Nuffield.—p. 424.

Acute Idiopathic Oedema in Early Childhood. E. P. Silberstein.—p. 435.

2, No. 13 (Sept. 28) 1957

A Course in Social Paediatrics to Medical Undergraduates. F. W. Clements.—p. 449.

Turner's Syndrome, Twenty Years After Treatment. Zelman Freeman.—p. 457.

**A Biochemical Approach to Calomel-Induced Mercurialism and to the Aetiology of Pink Disease.**—The author made a brief preliminary report which was abstracted in these pages. The present report concerns itself with the production of mercurial poisoning in animals when the intestinal tract is made more alkaline than usual. The author postulates from animal work, as well as from a review of the world literature, that acrodynia occurs in children ingesting calomel (mercurous chloride) when certain predisposing conditions exist. These conditions include achlorhydria caused by intercurrent infection or prolonged undernutrition and the presence of certain bacteria in the intestinal tract increasing its alkali. One of these organisms the author describes is Proteus mirabilis, which is proteolytic. Some of the symptoms of acrodynia may be due to interference with the action of vitamin $B_6$, whose action is inhibited by mercury. The author further states that some cases of pink disease may occur in the absence of mercurials, owing to a decrease in intestinal absorption of essential nutrients.

**The Use of Chlorpromazine to Control Spasm and Rigidity in Tetanus: Report of a Case.**—A case of tetanus of moderate severity is described in which chlorpromazine given parenterally produced good muscular relaxation and sedation. The relaxant effect was immediate and prolonged. The authors used six- to eight-hour intravenous injections, since intramuscular injections did not produce satisfactory relaxation during the height of the disease. Dosage of the drug varied from 20 to 40 mg. The patient was a well-developed and well-nourished adult. Following injection there was a slight drop in blood pressure but never to a dangerous level. The author suggests further trial of this drug for the treatment of tetanus.

## Metabolism, New York

**Abstracted by S. A. Kaplan, M.D.**

6, No. 6, (Nov., Pt. 2) 1957

* *Symposium on Intravenous Fat Emulsions*

Composition, Preparation and Testing of an Intravenous Fat Emulsion. Curtis E. Meyer, James A. Fancher, Paul E. Schurr, and H. D. Webster.—p. 591.

Effect of Parenterally Administered Fat Emulsion on Nitrogen Retention: Attempts at Complete Parenteral Alimentation in Dogs. Robert S. Levine, Ellen C. Calvary, Janice E. Plzak, and J. Garrott Allen.—p. 597.

Metabolic Studies of Intravenous Fat Emulsion in Normal and Malnourished Patients. Harold L. Upjohn, Morton C. Creditor, and Stanley M. Levenson.—p. 607.

Incidence of Reactions to an Intravenous Fat Emulsion Administered at Two Different Rates. Allan L. Forbes.—p. 645.

A Clinical Evaluation of an Intravenous Fat Emulsion. Wayne W. Glas and Carl H. Birkelo.—p. 650.

Intravenous Administration of an Improved Fat Emulsion. Paul H. Jordan Jr.—p. 656.

Clinical Experience with Intravenous Fat Emulsions. H. L. Lehr, O. Rosenthal, H. M. Rawnsley, J. E. Rhoads, and Marie Barnes Sen.—p. 666.

Experience with Administration of an Intravenous Fat Emulsion to Surgical Patients. John M. Beal, Mary Ann Payne, Helen Gilder, George Johnson, and William L. Craver.—p. 673.

The Protein-Sparing Effect of Intravenous Fat Emulsion. Curtis P. Artz and Thomas K. Williams.—p. 682.

Effect of Intravenously Administered Fat on Body Weight and Nitrogen Balance in Surgical Patients.

William E. Abbott, Harvey Krieger, William D. Holden, John Bradshaw, and Stanley Levey.—p. 691.
Observations on the Use of Intravenous Fat Emulsions in Man. Richard C. Borian, Norman W. Davidson, Leonard J. Stutman, and Charles F. Wilkinson Jr.—p. 703.
Clinical Studies on Intravenous Fat. Mark E. Smith.—p. 717.
Experience with the Use of Intravenous Fat Emulsions in the Treatment of Chronic Uremia. Roland E. Schneckloth, Harriet P. Dustan, and A. C. Corcoran.—p. 723.
Tolerance of Infants and Children to Fat Administered Intravenously. Robert Kaye, Margaret L. Williams, and Mitio Kumagi.—p. 727.
Use of Intravenous Fat in Burned Patients. Benjamin H. Gaston.—p. 735.
Some Effects of Multiple Intravenous Infusions of a Cottonseed Oil Emulsion in Patients with Laennec's Cirrhosis of the Liver. Fred Kern Jr., Robert G. Jackson, Theodore E. Martin, and John F. Mueller.—p. 743.
Effects of Repeated Infusions of a Fat Emulsion in Surgical Patients. Frederick W. Preston, Anne U. Barnes, Emanuel E. Mandel, Charles J. Staley, and Otto H. Trippel.—p. 758.
Clinical and Chemical Evaluation of Intravenous Fat Emulsion with Particular Reference to Changes of Serum Electrolytes. Gerald H. Becker and Melvin Buxbaum.—p. 766.
Further Observations on Fat Emulsion for Intravenous Infusion: Experience with Total Parenteral Nutrition Using Lipomul-I. V. Edwin H. Ellison and Edwin C. Mueller.—p. 774.
Clinical, Chemical, Hematologic and Anatomic Changes Accompanying Repeated Intravenous Administration of Fat Emulsion to Man. Donald M. Watkin.—p. 785.
Two Severe Reactions Following the Long-Term Infusion of Large Amounts of Intravenous Fat Emulsion. Stanley M. Levenson, Harold L. Upjohn, and Thomas W. Sheehy.—p. 807.
Clinical Observations on the Use of Nonphosphatide (Pluronic) Fat Emulsions. William R. Waddell, Robert P. Geyer, F. Russell Olsen, and Frederick J. Stare.—p. 815.
Army Medical Service Requirements for a Fat Emulsion Suitable for Intravenous Administration. Tyron E. Huber.—p. 822.
Final Discussion and Summary of the Conference on Intravenous Fat Emulsions.—p. 823.

**Symposium on Intravenous Fat Emulsions.**—After some delay it now appears that there has been developed an injectable emulsified fat suspension suitable for widespread use for injection intravenously. The preparation is Lipomul-I. V. and is manufactured by The Upjohn Company, Kalamazoo, Mich. The product is supplied in 600 ml. quantities and is made up of the following constituents: cottonseed oil (special) 15%, phosphatides (purified soya lecithin) 1.2%, Fluronic F68 (polyoxyethyleneoxypropylene emulsifier) 0.3%, and dextrose 4%. The aqueous phase and solvent is water. The caloric yield is 160 Cal. per 100 ml., and the pH of the solution is 4.4 to 4.9. Approximately 90% of the fat is present as particles which are submicroscopic. Less than 0.02% of the visible particles are over 1.5$\mu$ in diameter. The emulsion is physically and biologically stable for at least one year when stored in the refrigerator.

Infusion of Lipomul-I. V. into healthy adults does not produce changes in body weight; sodium-potassium balances; plasma urea, sodium, potassium, and protein; plasma and red blood cell volumes; circulating hemoglobin, and renal function. When 1200 ml. was infused daily for three weeks into a healthy man eating a basal maintenance diet, there was a sharp and sustained increase in nitrogen retention and body weight. In malnourished subjects infusion of the preparation resulted in weight gain and nitrogen retention

Among the untoward reactions the commonest is fever. Severe pyrogenic reaction, however, is uncommon. For example, in one series there were only 2 pyrogenic reactions in 129 infusions. Nausea and vomiting occurred in three instances. Severe reactions in general appear to be rare.

The preparation has been administered to patients who have recently undergone surgery with encouraging results. The emulsion also appears to be a safe and useful adjunct (at least for short periods) in the conservative medical management of chronic renal disease.

Kat et al. reported that they had given 250 infusions to 124 children aged 10 days to 13 years at a rate of 3 to 7 ml. per kilogram per hour for periods of four to six hours. Elevations of temperature by more than 2 degrees occurred in 21%, especially when the rate of infusion exceeded 5 ml. per kilogram per hour. Vomiting occurred in about 1 out of every 10 cases. No other severe reactions occurred.

The emulsion has also been administered to patients with Laennec's cirrhosis and with burns. In general, the responses were favorable.

## Monatsschrift für Kinderheilkunde, Berlin

**Abstracted by Hans Hartenstein, M.D.**

105:201-240 (June) 1957

Toxoplasmosis in Childhood: Clinical and Serological Observations. Horst Verse.—p. 201.
Reactions Following Treatment of Septicemia with Antibiotics. H. Stickl and A. Kerstien.—p. 208.

Agammaglobulinemia in Childhood. F. Koch, G.-W. Schmidt, and E. Doll.—p. 211.
Taussig-Bing Complex with Pulmonary Stenosis. K. Bock, D. Nichel, and M. Herbst.—p. 219.
Proceedings of the Federation of Pediatricians of the Rhineland and Westphalia, Held on Nov. 3, 1956, in Düsseldorf, Germany.—p. 222.
Review Article: Recent Attempts to Influence Natural Resistance to Infections and Susceptibility to Infections by Nutrition. J. Jochims.—p. 225.
The Newborn and Premature Infant. Hans Ewerbeck.—p. 229.

105:241-280 (July) 1957

* Epidemics of Abacterial Meningitis in Rural Areas and Isolated Settlements. Johannes Brockhaus and Irmgard Kruse.—p. 241.
Electronic-Optic Investigations on the Colloidal Structure of Infant Foods. Erich Huth.—p. 247.
Renal Clearance in Childhood: Comparative Studies with Various Clearance Methods. Hanns-Juergen Rohwedder.—p. 249.
The Significance of Para-Nasal Sinus Disease in Childhood. Kurt Nitsch.—p. 251.
Bronchial Asthma in Childhood: Results of Follow-Up Studies in 500 Patients. Gustav-Adolf v. Harnack and Brigitte Panten.—p. 255.
Experiments Using a Combination of Isoniazid and a Heterocyclic Thiosemicarbazone. G. Jannsen, H. G. Stammler, and F.-J. Pothmann.—p. 258.
The Diagnostic-Prognostic Value of Repeated Intracutaneous Tuberculin Tests. Kurt Lother.—p. 261.
The Electrocardiogram of Premature Infants Kept at Low Body Temperatures. Gerhard Joppich and Joachim Stoermer.—p. 264.
About a Peculiar Osteopathy in an Infant, Difficult to Classify. Robert Berkman.—p. 267.
Newborn and Premature Infants. Hans Ewerbeck.—p. 272.

**Epidemics of Abacterial Meningitis in Rural Areas and Isolated Settlements.**—An epidemic of meningitis which occurred in the fall of 1956 in many parts of Eastern Westphalia, Germany, is reported. The disease was commoner among children and adolescents of the rural population. It was highly contagious; the incubation period varied from 11 to 15 days, and the prognosis was favorable. The disease showed a familial spread and was observed two times among the population of children's hospitals; these observations suggested a direct transmission by close contact from person to person. Latent and asymptomatic forms may have occurred frequently, and these may explain the spread of the disease. This form of meningitis was classified among the "poliomyelitis-like" diseases because of the many features which this new disease had in common with poliomyelitis, i. e., the incubation period, occurrence in siblings, the ratio between fully developed and abortive and asymptomatic forms, a tendency to occurrence in young persons, distribution in rural and urban areas, seasonal variations, and the occurrence of sporadic cases after the peak of the epidemic.

Of 85 patients reported on, 45 had a diphasic course; pain in the neck and back, vomiting, and fever were the predominant symptoms. The number of cells in the cerebrospinal fluid varied from 50 to 8800 per cubic centimeter and was not related to the severity of the disease. The pathogenesis of the disease has not been elucidated. Myeloencephalic processes apparently occurred in addition to the meningitic process in some patients, but the encephalitic manifestations were as a rule benign. A neurotropic virus with biological properties similar to those of the poliomyelitis virus is probably the causative agent.

## New England Journal of Medicine, Boston

**Abstracted by Demetrius G. Traggis, M.D.**

257, No. 7 (Aug. 15) 1957

* Staphylococcal Infections in an Obstetric Unit: I. Epidemiologic Studies of Pyoderma Neonatorum. D. N. Wysham, M. E. Mulhern, G. C. Navarre, G. D. La Veck, A. L. Kennan, and W. R. Giedt.—p. 295.
Staphylococcal Infections in an Obstetric Unit: II Epidemiologic Studies of Puerperal Mastitis. D. N. Wysham, M. E. Mulhern, G. C. Navarre, G. D. La Veck, A. L. Kennan, and W. R. Giedt.—p. 304.
An Unusual Receptive Aphasia as a Manifestation of Temporal-Lobe Epilepsy: Report of Case Treated by Surgery. A. Solomon.—p. 313.
Importance of Detecting Rapid Changes in Blood Catechol Amine Levels in the Diagnosis of Pheochromocytoma. F. W. Reutter, M. S. Zileli, J. T. Hamlin, G. W. Thorn, and D. G. Friend.—p. 323.

**Staphylococcal Infections in an Obstetric Unit: I. Epidemiologic Studies of Pyoderma Neonatorum.**—The authors refer to the epidemics of staphylococcal infections in nurseries in Seattle. Of 174 live births in one hospital, 22% were complicated by clinical staphylococcal infections, including five breast abscesses, of which one was fatal. Careful scrutiny of nursery techniques did not reveal any changes that should be made. This latter observation, made by other workers as well, has lead to the concept that the spread of Staphylococcus in a nursery may be independent of nursery personnel and their techniques. Substantiating this was the finding in the one hospital that a large number of infants were

colonized by a single strain of staphylococci not carried by the nursery personnel. Others have reported similar findings. These findings have suggested that the organism is spread from infant to infant, probably via nursery air. In order to find out the manner of spread, the authors undertook an investigation of the epidemiology of staphylococcal spread in the hospital.

Cultures were taken on mothers from nose and vagina on admission and from nose, hands, and breast every day for five days post partum and then at two and six weeks. Cultures were taken from the nose, throat, and skin of all infants daily for five days and at two and six weeks. Cultures were also taken on several occasions from all the presonnel on the obstetric floor and nurseries. In addition, specimens were taken from fomites in the nursery and obstetric floor and also from room air. Phage typing, combined with determination of antibiotic sensitivity was judged the best way to identify the staphylococci found. In general, the aseptic technique used was very good. The infants were not bathed in the nursery, and no lotions, ointments, or antiseptic detergents were used on their skin.

Of 117 infants followed, 54 (or 46%) manifested clinical staphylococcal infections during the first six weeks of life. There were 51 skin infections, of which 28 were due to the epidemic strain, and 1 infection each of conjunctivitis, otitis media, and septicemia, none of which were due to the epidemic strain. The shape of the curve of age onset of clinical cases showed that the hospital was the source. Curves of colonization showed that 81 infants (or 69%) were colonized before discharge, of which 49 were colonized by the epidemic strain. There was a slight increase in the number on the first return visit. Sources of infection which were eliminated by negative cultures or by the infant's having a different strain of Staphylococcus than the suspected source were mother's vagina, bedding of mothers, obstetricians, the mother's nose and throat (none positive for infant's strain on entering hospital), and the nursery personnel. This left only the infants. On the average, they stayed in the hospital 2.8 days after colonization and were often heavily infected. Cultures of their bedding showed heavy infestation. It was noted that often in changing infants the blanket was shaken in air near or over another infant. The nurses hands were cultured and were usually found to be negative. Samples of room air showed very few organisms present when nursery was quiet before the day's activity. During general activity the count increased two and one-half times, and during changing of bedding it increased five times (of which one-half the colonies were epidemic strain). As to method of colonization of infants, it was found that 30% had the organism first in nose and throat, while the skin was negative; in 25% both skin and respiratory tract became positive simultaneously, and in the rest the skin became positive first.

Other factors noted were that with a high census about 90% of the infants were colonized whereas with a low census only 20% of the infants were colonized. After a three-day period when no infants were in the nursery, the epidemic seemed to stop. Furthermore, when rooming-in was used only a few infections occurred, but when it became necessary to discontinue rooming-in another, although smaller, outbreak occurred.

Thus it appears that the infants are the source of the Staphylococcus and colonize each other, particularly since in many nurseries infants of various ages are in the same room. The authors feel that use of a detergent containing hexachlorophene for bathing infants is not satisfactory because it does not prevent the colonization of the nose and throat. It does help somewhat as far as skin contamination is concerned. They also feel that antibiotics orally are not the answer because of the ease with which the organism becomes resistant, a fact which has already appeared in this area when it was discovered that in one hospital erythromycin-resistant staphylococci were now being isolated. The authors also feel that careful nursery techniques, rooming-in, and rearrangement of nurseries by having more rooms available so that infants of different ages are not exposed to each other offer perhaps the best methods of preventing these epidemics. The authors also state that they feel that staphylococcal infections are contagious via air, as well as possibly on hands, and that this may account for the prevalence of staphylococcal infections in hospitals in other places besides nurseries, as on surgical floors.

## Pediatriya, Moscow

### No. 8, 1957

The Role of Biochemistry in the Study of Certain Childhood Diseases. A. A. Titaev.—p. 3.
Toxoplasmosis as a Problem in Medicine.—G. Vildfyur.—p. 12.

Cardiovascular Changes in Diphtheria. V. S. Ushakova.—p. 24.
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* Physical Development of Children in the First Year of Life in Moscow, 1956. R. Kogan.—p. 67.
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* Fluctuation of Arterial Blood Pressure in Bronchial Asthma. N. A. Tyurin.—p. 41.
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Immunologic Response in Infants with Pneumonia Treated with Antibiotics. S. L. Dub and R. M. Evantova.—p. 55.
Physiotherapy in the Treatment of Pneumonia in Early Childhood. G. P. Yurko.—p. 62.
Infant Mortality Due to Pneumonia and Gastrointestinal Diseases in the City of Orel, 1948-1956. E. I. Albats.—p. 77.
Experience in Lowering Childhood Mortality in Pneumonia. T. G. Petrova.—p. 80.

**Physical Development of Children in the First Year of Life in Moscow, 1956.**—In the course of the year 1956, there were 3500 children from all districts of Moscow who were seen in the child-care centers and were carefully measured to establish new norms and to compare them with previous determinations performed in 1937. Comparison between the two studies revealed that by 6 months of life, the average weight was increased by 500 gm.; by 1 year, by 925 gm. Length by 6 months of age was increased by 1.5 cm.; by a year, by 2 cm. Chest circumference by 1 year was increased by 2 cm.; head circumference, by 1 cm. Factors contributing to this better physical development are discussed.

Another finding of the study was that the greatest increments in height and weight occurred not in the first month of life but in the second one—the increments being 1078 gm. and 4.4 cm. in boys and 843 gm. and 3.8 cm. in girls. The drop-off in increments of height and weight occurred in the third month of life. Doubling of weight occurred at 4½ months of age and tripling by 1 year. Head and chest circumference became equal between the second and third months of life. Average daily weight gain is comparable to that reported in Western literature. The authors suggest that the new norms which they have published should be used as normal values in child-care centers of Moscow and that area of the country.

**Fluctuation of Arterial Blood Pressure in Bronchial Asthma.**—Throughout the years 1955-1956 in the children's service of the First Moscow Medical Institute, studies were performed on the cardiopulmonary physiology in children with bronchial asthma. Forty-six children with bronchial asthma were studied extensively.

This paper reports only the fluctuation of arterial blood pressure which was noted. The method entailed determining blood pressure while the child was lying down. First a number of determinations were performed to get the child used to the procedure and to obtain a baseline pressure. When the pressure was gradually lowered in the mercury manometer, it was noted that auscultatory sounds came through only in expiration; as the mercury was lowered further one began to hear the sounds in inspiration also. The significant difference in arterial blood pressure between expiration and inspiration was denoted as inspiratory-expiratory difference. It was noted that in normal children, in the absence of dyspnea, this difference was 3 to 5 mm.; with minimal dyspnea, even if the child was not aware of his difficulty, this inspiratory-expiratory difference was increased to 8 to 10 mm. In some of the severer cases the difference was as much as 40 to 45 mm. of mercury.

The author reviews some work performed in Russia on animals, showing relation of intrapulmonary pressure to arterial blood pressure. They believe that fluctuations in arterial pressure are due to two factors: (1) the factor of intrapulmonary pressure and (2) the effect of the central nervous system, which is certainly involved in an acute attack of bronchial asthma. Their conclusion is that the inspiratory-expiratory blood pressure difference is an objective method of measuring severity of dyspnea in bronchial asthma and that this inspiratory-expiratory difference usually precedes the onset of the acute attack.

# News and Comment

## ANNOUNCEMENTS

**Third International Congress of Allergy.**—The Third International Congress of Allergy, sponsored by the International Association of Allergology and French Allergy Association, will be held in Paris, France, Oct. 19-26, 1958. The program will include (*a*) Symposia on asthma and emphysema, immunology, recent clinical advances, biochemical aspects, autoimmune reactions, dermatology, and socioeconomic aspects. Participants are world authorities in special fields: Pasteur Vallery-Radot, Löffler, Grabar, Dixon, Chase, Coombs, Forsham, Sir Henry Dale, Halpern, Schild, Harrington, Ackroyd, Dausset, Zondek, Sulzberger, Jadassohn, and many others; (*b*) sectional papers, limited to 10 minutes, on any phase of allergy; (*c*) round-table small-group luncheon conferences on selected subjects led by international authorities; (*d*) pre- or postconvention tours; (*e*) social meetings; a very enjoyable program has been arranged.

For all information regarding the program and papers to be presented please write to the following persons.

United States and Canada: Dr. Samuel M. Feinberg, 303 E. Chicago Ave., Chicago.

Latin America: Dr. José M. Quintero Fossas, Paseo 313, Vedado, Havana, Cuba.

Europe and other countries: Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris 7, France.

For Congress information and registration write to Dr. Halpern at the above address. The registration fees are $32 for congressists and $15 for associate participants (relatives).

Arrangements for travel and for pre- or postconvention tours can be made through Thos. Cook and Sons.

**National Foundation for Infantile Paralysis: Fellowships for Tissue-Culture Course.**—The National Foundation for Infantile Paralysis is again offering fellowships to post-doctoral investigators, teachers, and graduate students and experienced laboratory personnel with the baccalaureate degree for participation in short courses in tissue culture.

Fellowships may be used for study only in formal courses designed to teach the principles, techniques, and application of tissue culture. Funds will be awarded for the period necessary to complete the course, which, in most instances, is not expected to exceed six weeks.

Financial assistance, based on individual need, may include an allowance for maintenance, for tuition and fees, and for round-trip transportation.

Further information and application forms may be obtained from the Division of Professional Education. Completed application should reach the National Foundation at least six weeks prior to the beginning of the course. Write to Division of Professional Education, National Foundation for Infantile Paralysis, 301 E. 42d St., New York 17.

**Fellowships in Infant and Child Development.**—Fellowships in developmental diagnosis are available at the Clinic of Child Development, which is sponsored jointly by the Department of Pediatrics of The Ohio State University, College of Medicine; the Children's Hospital of Columbus, Ohio, and the State Department of Mental Hygiene and Correction. The Clinic is concerned with the evaluation of neurologic status and maturity level in children in the preschool period suspected of having deviations in development. The majority of the children have neuropsychiatric disabilities which are organic in nature. In addition to diagnostic evaluation, guidance in the management of problems and help in securing the necessary medical and community services is provided.

Fellowships are open to pediatricians or psychiatrists who are board-eligible. They are for a period of one year, beginning July 1, 1958, with one position available each six months, and they carry a stipend of $5000. Physicians who are trained will have opportunities to engage in research projects designed to elucidate the etiologies of the neuropsychiatric disabilities of childhood and to enter into the teaching program.

Address inquiries to Dr. Earl H. Baxter, Chairman, the Department of Pediatrics, The Ohio State University, or to Dr. Hilda Knobloch, Director of the Clinic of Child Development, Children's Hospital, 561 South 17th St., Columbus 5, Ohio.

**New Award For Medical Writing.**—The editors of *Modern Medical Monographs*, a quarterly publication, announce an award for the best unpublished manuscript for a short book on a clinical subject in the field of internal medicine. The purpose of this award, which will be known as the Modern Medical Monograph Award, is to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing. The winner of this competition will receive $500. In addition, the winning monograph, if found suitable, will be published as a book in the series *Modern Medical Monographs*. The generosity and cooperation of Dr. Henry M. Stratton, President of Grune & Stratton, Inc., publishers of the series, have made this award possible.

The entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association and for clinical interest and scientific value by the Editors and Advisory Board of *Modern Medical Monographs*.

1. The author, or authors, must be a graduate physician, less than 40 years of age. Single authorship is preferred, but two co-authors will be acceptable. The name of the medical school from which the author graduated and his date of graduation should be stated.

2. Manuscripts should be submitted in duplicate (original and one copy) by registered mail, postmarked no later than Oct. 1, 1958, to Richard H. Orr, M.D., 37 E. 67th St., New York 21.

3. The manuscript, including the bibliography, must consist of between 115 and 200 double-spaced typewritten pages with ample margins and not more than 40 illustrations (figures or photographs). For each illustration used, the allowable upper limit of typewritten manuscript pages should be reduced by one.

4. Fishbein's book, "Medical Writing" (third edition), should be followed in preparation of the manuscript, use of abbreviations, and bibliographic form.

**IX International Congress of Paediatrics.**—The IX International Congress of Paediatrics will be held in Montreal July 19 to 25, 1959. All correspondence to the President, Prof. Alan Ross, or the Secretary General, Dr. R. L. Denton, should be addressed to P. O. Box 215 Westmount, Montreal 6, Canada.

**Summer Camp for Diabetic Children.**—The Summer Camp for Diabetic Children will be conducted for the tenth year under the auspices of the Chicago Diabetes Association from July 20 through Aug. 10, at Holiday Home, Lake Geneva, Wis. Boys and girls from 8 through 14 years of age are eligible.

As in previous years, the camp will be staffed by resident physicians, a nurse, two dietitians, and a laboratory technician, in addition to the regular counseling and domestic staff of Holiday Home.

Rates for summer camp are arranged in accordance with individual circumstances.

Applications may be obtained from, and inquiries should be addressed to, The Chicago Diabetes Association, 5 S. Wabash Ave., Chicago 3.

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Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

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* Fries, J. H., Milk Allergy-Diagnostic Aspects and the Role of Milk Substitutes, J.A.M.A., Nov. 23, 1957.

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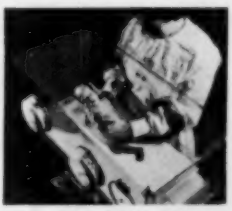

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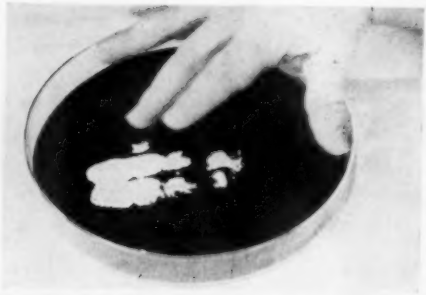

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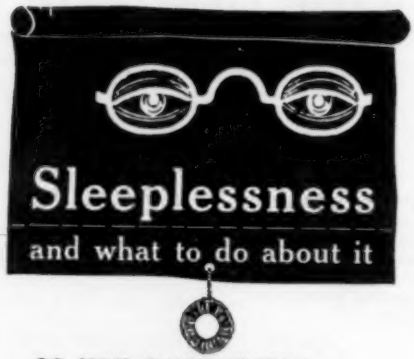


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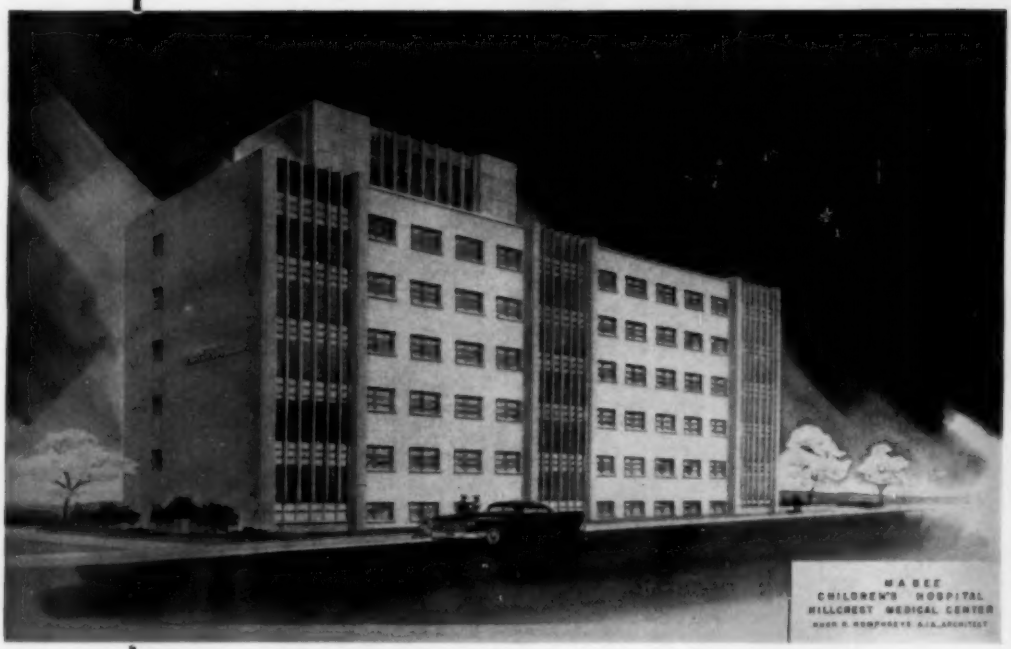


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KIDS LOVE 'EM*

*WORMS HATE 'EM

**No fasting • No special diets • No purging**

The new Piperazate Wafers, utilizing insoluble piperazine *phosphate*, provide short, pleasant piperazine treatment for intestinal helminths. For pinworm, *only one dose a day* for just *one week* is required; for roundworm, *a single dose*.

Kids love the cool, tasty mint flavor of Piperazate Wafers. There is no possibility of spillage or variation in the size of the dose. And the use of Piperazate avoids the high incidence – 35-50% – of nausea, vomiting and diarrhea which may be associated with gentian violet therapy.[1]

Piperazate assures a 90% cure rate in one week's treatment of pinworm[2] and an 85% cure rate in one day's treatment of roundworm.[3]

| One Week Dosage for Pinworm | One Day Dosage for Roundworm |
|---|---|
| Children 15-30 lbs. . . . 1 Wafer | Children 20-30 lbs. . . . 3 Wafers |
| Children 31-60 lbs. . . . 2 Wafers | Children 31-40 lbs. . . . 4 Wafers |
| Children 61 lbs. and over . . . . . 4 Wafers | Children over 40 lbs. and adults . . . . . 7 Wafers |
| To be sucked or chewed before breakfast for 7 consecutive days. | To be taken at one time on one day only. |

# Piperazate* Wafers

piperazine phosphate, Leeming, 500 mg.

Supplied: In packages of 28 Wafers

1. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, Macmillan, 1955, p. 1153. 2. Brown, H. W., *et al.*: J.A.M.A. *161*:515 (June) 1956. 3. Hoekenga, M. T.: World M. J. 3:299 (Sept.) 1956.

*TRADEMARK

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**Prompt and**
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**NO STING • NO SEDATION • NO EXCITATION**
**In practically all patients**
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